JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 5, 2008
OCTOBER 2008:524–32

viewed and adjudicated by an independent Clinical Events Committee whose members were unaware of treatment allocation. An independent Data and Safety Monitoring Board periodically reviewed blinded safety data.

The trial was designed to show noninferiority of in-segment late loss after 9 months (expected difference in means, μZoMaxx Stent − μTaxus Stent = 0), with a noninferiority margin of 0.25 mm and a standard deviation of 0.4 mm. Late luminal loss was defined as the difference between the MLD immediately after stenting and at follow-up. Because late loss values <0.6 mm for stented arteries between 2.5 and 3.5 mm in diameter have little clinical consequence, and the Taxus stent can be expected to generate 0.23 ± 0.44 mm in-segment late loss in this lesion cohort (2), a noninferiority margin of 0.25 mm was considered clinically and statistically appropriate. The trial was 99% powered to detect noninferiority with a 1-sided p value of 0.05.

Other treatment group comparisons were performed using the 2-sample *t* test for continuous variables, Fisher exact test for dichotomous variables, and Cochran-Mantel-Haenszel (Modified Ridit scores) for ordinal variables with more than 2 categories. Univariate and multivariate logistic regression was performed on the binary TVR results to understand the predictive value of several covariates. For the multivariate logistic regression, predictors were chosen by stepwise linear regression using an entry criteria of 0.2 and a stay criteria of 0.1.

Results

Four-hundred and one patients were enrolled sequentially in the study from 29 clinical sites in Europe, Australia, and New Zealand (Appendix). The first patient was enrolled on September 14, 2004, and the final patient was enrolled on July 18, 2005. Five patients (4 randomized to ZoMaxx and 1 randomized to Taxus) were subsequently deregistered after randomization and did not receive a study stent (3 were deemed to be ineligible after randomization, 1 sustained a complication before stent insertion, and 1 withdrew consent before stent insertion). This left a total of 396 patients for analysis (199 ZoMaxx and 197 Taxus).

The clinical and lesional demographics of the 2 patient cohorts are given in Table 1. The groups were fairly well matched demographically, as there were similar frequencies of diabetes (ZoMaxx 22% vs. Taxus 26%) and unstable angina (ZoMaxx 26% vs. Taxus 24%). However, there was statistically significantly more intervention in the right coronary artery in the Taxus group versus the ZoMaxx group (41% vs. 28%; p = 0.008). Furthermore, 8 lesions in the ZoMaxx group were ostial in location (within 2 mm of their origin); there were no ostial lesions in the Taxus group (4.0% vs. 0%; p = 0.0007).

Post-procedure metrics are given in Table 2. Lesion and device success were 99% for both stents (p = NS). There were no differences with respect to post-procedure in-stent or in-segment MLD, percent diameter stenosis, or acute gain between the 2 groups.

Table 1. Clinical and Lesional Demographics of Patients Enrolled in the ZoMaxx I Trial

	ZoMaxx (n = 199)	Taxus (n = 197)	p Value
Age (yrs)	63 ± 10	63 ± 11	NS
Male gender	75%	77%	NS
Diabetes	22%	26%	NS
IDDM	8.0%	8.6%	NS
Unstable angina	26%	24%	NS
Hypercholesterolemia	78%	72%	NS
Hypertension	69%	67%	NS
Family history of premature CAD	39%	34%	NS
Current smoker	24%	19%	NS
Prior MI	29%	29%	NS
Prior PCI	20%	25%	NS
Prior CABG	4.5%	1.0%	NS
LVEF	65% ± 12%	65% ± 11%	NS
Vessel location			0.025
LAD	48%	40%	
LCX	24%	19%	
RCA	28%	41%	*
Lesion location			0.031
Ostial	4.0%	0.0%	†
Proximal	39%	41%	
Mid	51%	51%	
Distal	6.0%	8.6%	
Lesion length (mm)	14.9 ± 5.7	14.6 ± 5.5	NS
RVD (mm)	2.79 ± 0.43	2.81 ± 0.46	NS
Total stent length (mm)	21.3 ± 5.9	20.8 ± 5.7	NS
Stent-to-lesion ratio	1.6 ± 0.6	1.6 ± 0.6	NS
Stents per patient	1.1 ± 0.4	1.1 ± 0.3	NS

*RCA vs. other locations, p = 0.008. †Ostial vs. other locations, p = 0.007.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; IDDM = insulin-dependent diabetes mellitus; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; RVD = reference vessel diameter.

Angiographic results are given in Table 3. Nine-month in-segment late lumen loss (primary end point) was 0.43 ± 0.60 mm and 0.25 ± 0.45 mm in the ZoMaxx and Taxus angiographic cohorts, respectively; the observed difference in the means was 0.18 mm. The distributions of in-segment late lumen loss in the ZoMaxx and Taxus groups are shown in Figure 3. Because the upper bound of a 95% confidence interval on the difference in the means (0.27 mm) was larger than the pre-specified noninferiority limit (0.25 mm), the primary angiographic end point of noninferiority of in-segment late lumen loss was not met. Consistent with the in-segment late loss results, in-segment binary restenosis was greater in the ZoMaxx group than in the Taxus group (16.5% vs. 6.9%; p = 0.007).

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 5, 2008
OCTOBER 2008:524–32

Table 2. Post-Procedural Results in the ZoMaxx I Trial

	ZoMaxx (n = 199)	Taxus (n = 197)	p Value
Lesion success	198 (99%)	195 (99%)	NS
Device success	197 (99%)	194 (99%)	NS
Procedure success	188 (95%)	189 (96%)	NS
In-stent	(n = 170)	(n = 175)	
MLD (mm)	2.71 ± 0.39	2.72 ± 0.43	NS
Diameter stenosis (%)	4.6 ± 7.9	4.4 ± 8.5	NS
Acute gain (mm)	1.90 ± 0.41	1.96 ± 0.49	NS
In-segment	(n = 170)	(n = 175)	
MLD (mm)	2.29 ± 0.47	2.29 ± 0.49	NS
Diameter stenosis (%)	20 ± 9.7	20 ± 9.5	NS
Acute gain (mm)	1.49 ± 0.45	1.53 ± 0.51	NS

MLD = minimum lumen diameter.

Similarly, in-stent late lumen loss was found to be statistically significantly greater after ZoMaxx stenting as compared with Taxus stenting (0.67 ± 0.57 mm vs. 0.45 ± 0. 48 mm; $p < 0.0001$), resulting in a higher frequency of in-stent restenosis in the ZoMaxx group (12.9% vs. 5.7%; $p = 0.025$). Even using nonparametric analysis, more appropriate for non-normal distributions such as late loss after implantation of DES (25,26), the difference in the medians remained statistically significant (median in-stent late loss ZoMaxx 0.58 mm vs. Taxus 0.41 mm; $p < 0.05$ using the Kruskal-Wallis test).

Clinical results at 9 months encompassing all follow-up angiography performed up to 284 days are given in Table 4; 9-month clinical follow-up was available in 96% of patients (382 of 396). There were no significant differences between treatment groups for any clinical end point. The rate of TLR was nearly double in the ZoMaxx group as compared with the Taxus group (8.0% vs. 4.1%), although the difference did not reach statistical significance (p = NS). There were no differences in the incidence of stent thrombosis whether protocol-defined (0.5% in both groups) or retrospectively applying the definitions suggested by the Academic Research Consortium (27) (1.0% in both groups).

Table 3. 9-Month Angiographic Results in the ZoMaxx I Trial

Angiographic Results	ZoMaxx (n = 170)	Taxus (n = 175)	p Value
In-stent			
MLD (mm)	2.03 ± 0.63	2.27 ± 0.58	<0.001
Diameter stenosis (%)	27 ± 21	19 ± 17	<0.001
Late loss (mm)	0.67 ± 0.57	0.45 ± 0.48	<0.001
Restenosis (%)	12.9	5.7	0.025
In-segment			
MLD (mm)	1.86 ± 0.59	2.04 ± 0.55	0.004
Diameter stenosis (%)	34 ± 19	28 ± 14	<0.001
Late loss (mm)	0.4 ± 0.60	0.25 ± 0.45	0.003
Restenosis (%)	16.5	6.9	0.007

MLD = minimum lumen diameter.

The IVUS results are given in Table 5. Neointimal volume obstruction by IVUS was statistically significantly greater after ZoMaxx stenting (14.6 ± 7.9% vs. 11.2 ± 9.6 %; $p < 0.018$). The incidence of late acquired malapposition was slightly less after ZoMaxx stenting, although the difference did not reach statistical significance (0% vs. 3%; p = NS).

To evaluate the possible predictive value of covariates in the ZoMaxx I study, both univariate and multivariable logistic regression analyses were performed on the entire patient cohort to identify significant risk factors for the need for follow-up TVR. The results, shown in Table 6, identify only ostial lesion location ($p = 0.002$) and the presence of diabetes ($p = 0.003$) as statistically significant predictors of the need for TVR after 9 months.

Discussion

Although a variety of antiproliferative agents have been suggested as putative inhibitors of stent-induced restenosis, only sirolimus (1), paclitaxel (2), everolimus (3), and zotarolimus (28) have been proven safe and effective in large-scale, multicenter, randomized clinical trials. One compound, zotarolimus (formerly known as ABT-578, Abbott Laboratories) (Fig. 2), has been specifically developed for use in DES having no other systemic formulation or indication. Intravascular stents that elute zotarolimus have been shown to be effective in inhibiting in-stent restenosis both in experimental animal models (29) and in patients undergoing percutaneous coronary intervention (4,28).

To date, 4 zotarolimus-eluting devices have been tested clinically: the Prefer (Abbott Laboratories) (30), Endeavor (Medtronic, Minneapolis, Minnesota), (4) ZoMaxx (31), and Resolute (Medtronic) (32) stents. The most extensively

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 5, 2008
OCTOBER 2008:524–32

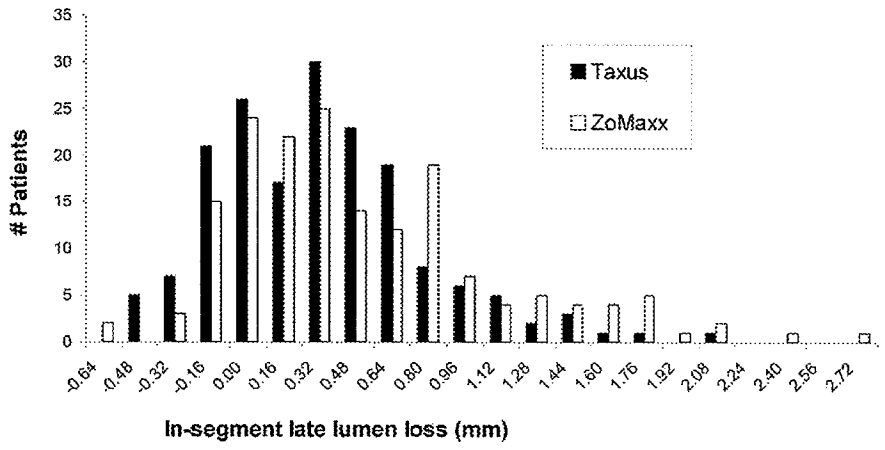


Figure 3. Distribution of In-Segment Late Loss in the Taxus and ZoMaxx Cohorts of the ZoMaxx I Trial

studied is the Endeavor stent, which also contains 10 μg/ml zotarolimus in a PC-based formulation that, in experimental animals, elutes approximately 95% of its drug load over about 15 days (4). The Endeavor II pivotal trial compared the Endeavor stent to the bare metal Driver stent in 1,200 patients, and the results showed highly statistically significant reductions in late lumen loss (in-stent 1.03 ± 0.58 mm vs. 0.61 ± 0.46 mm; $p < 0.0001$), angiographic binary restenosis (in-stent 33.5% vs. 9.4%; $p < 0.0001$), target vessel failure (15.1% vs. 7.9%; $p = 0.0001$) and MACE (14.4% vs. 7.3%; $p = 0.0001$) (28). Based on these and other clinical trial results (4,33,34), the Endeavor stent is now approved for clinical use worldwide.

The ZoMaxx stent was first tested clinically in the ZoMaxx IVUS trial, which enrolled 40 patients with symptomatic ischemic coronary occlusive disease at the Instituto Dante Pazzanese de Cardiologia in Saõ Paulo, Brazil (31). The lesion, procedure, and device-deployment success rates

Table 4. 9-Month Clinical Results in the ZoMaxx I Trial (Includes All Follow-Up Angiograms Performed Through 284 Days)

	ZoMaxx (n = 199)	Taxus (n = 197)	p Value
Q-wave MI	1.0%	0.5%	NS
Non-Q-wave MI	4.5%	4.1%	NS
TVR (ischemia-driven)	8.5%*	6.6%	NS
Cardiac death	0.0%	0.0%	NS
Total MACE†	12.6%	9.6%	NS
TLR	8.0%*	4.1%	NS
Non-TL TVR	2.5%	3.0%	NS
Target vessel failure	12.6%	9.6%	NS
All death	1.5%‡	0.0%	NS
Total stent thrombosis (protocol-defined)	0.5% (1)	0.5% (1)	NS
Acute stent thrombosis (24 h)	0.0%	0.0%	NS
Subacute stent thrombosis (1–30 days)	0.5% (1)	0.5% (1)	NS
Late stent thrombosis (>30 days)	0.0%	0.0%	NS
Total stent thrombosis (ARC-defined)	1.0% (2)	1.0% (2)	NS
Acute stent thrombosis (24 h)	0.5% (1)a	0.5% (1)b	NS
Subacute stent thrombosis (1–30 days)	0.0%	0.5% (1)a	NS
Late stent thrombosis (>30 days)	0.5% (1)c	0.0%	NS

*Includes 3 instances of TLR in ostial lesions. †MACE is a composite hierarchical end point of Q-wave MI, non–Q-wave MI, TVR, and cardiac death. ‡Three noncardiac deaths include 1 patient with acute renal and multiorgan failure at day 91, 1 patient with neuroendocrine malignancy at day 212, and 1 patient with intracerebral hemorrhage at day 274.

ARC = Academic Research Consortium (27); a = definite; b = probable; c = possible; MACE = major adverse cardiac events; TL = target lesion; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 5, 2008
OCTOBER 2008:524–32

Table 5. 9-Month IVUS Results in the ZoMaxx I Trial

	ZoMaxx (n = 114)	Taxus (n = 120)	p Value
Stent volume (mm^3)	155 ± 62	143 ± 58	NS
Lumen volume (mm^3)	132 ± 54	127 ± 55	NS
Neointimal volume (mm^3)	23 ± 16	16 ± 15	0.007
Neointimal volume obstruction (%)	14.6 ± 7.9	11.2 ± 9.6	0.018
Post-procedure SIA	19 (20%)	19 (19%)	NS
Persistent SIA	9 (9.6%)	10 (9.9%)	NS
Resolved SIA	10 (10.6%)	9 (8.9%)	NS
New (late-acquired) SIA	0 (0%)	3 (3.0%)	NS

IVUS = intravascular ultrasound; SIA = stent incomplete apposition.

were all 100% (40 of 40), and there was no MACE during the 4-month study. Follow-up angiography at 4 months showed in-stent and in-segment late lumen losses of 0.20 ± 0.35 mm and 0.17 ± 0.35 mm, respectively, with IVUS examinations showing a mean of 6.5 ± 6.2% neointimal volume obstruction. There were no instances of late acquired stent incomplete apposition or stent thrombosis. In comparison with a similar clinical trial using the nondrug TriMaxx stent studied angiographically at 6 months, the ZoMaxx stent significantly reduced in-stent restenosis from 25% to 2.7% (35).

These initial observations were extended through the ZoMaxx I clinical trial reported herein. The ZoMaxx I trial was designed to study a larger and more complex patient cohort with longer duration of follow-up in multinational geographies and to concurrently compare the outcome of ZoMaxx stent implantation with patients treated with the Taxus paclitaxel-eluting stent.

The ZoMaxx and Taxus patient groups in the ZoMaxx I trial were generally well-matched in both clinical and lesion characteristics. The exception was the preponderance of ostial lesions within the ZoMaxx cohort (n = 8) as compared with the Taxus cohort (n = 0). This occurrence was random and was uncovered as a result of retrospective core laboratory analysis of baseline angiograms, wherein lesions believed to be acceptable candidates for entry into the study were subsequently found to be within 2 mm of the artery's origin. It is known that percutaneous treatment of ostial occlusive lesions carries a substantially higher risk of restenosis (36–39), TVR (37), and 1-year mortality (40), and this is why patients with lesions that are located near one of the coronary ostia have been specifically excluded from pivotal clinical trials of DES (1,2,28). Indeed, the presence of an ostial lesion was the most significant multivariate predictor of TVR in the 386-patient cohort (p = 0.002), even slightly stronger than the presence of diabetes mellitus (p = 0.003).

The inclusion of patients with ostial lesions in the ZoMaxx group notwithstanding, there were no differences between the ZoMaxx and Taxus stent in device deployment or safety as shown by the high rates of device success (99% in both groups), a low stent thrombosis rate, and the absence of late stent thrombosis. There were no significant differences between treatment groups for any clinical metric that was evaluated (Table 4), although the study was not specifically powered to detect differences in infrequent events.

The most important finding in this clinical study was the statistically significant difference in late lumen loss between the 2 angiographic cohorts. The frequencies of both angiographic (87%) and IVUS (59%) follow-up are among the highest reported in any clinical trial of DES. After 9 months, patients treated with the ZoMaxx stent showed a mean in-segment late lumen loss of 0.43 ± 0.60 mm, whereas patients treated with the Taxus stent showed only 0.25 ± 0.45 mm of luminal loss (p < 0.001). Because the upper bound of a 95% confidence interval on the difference

Table 6. Univariate and Multivariate Logistic Regression Analysis of Predictors of TVR in the ZoMaxx I Trial

Predictor	Coefficient	SE	Odds Ratio	p Value
Univariate				
Diabetes	1.34	0.50	3.8	0.007
Lesion location (ostial vs. others)	2.11	0.86	8.3	0.014
Reference vessel diameter	−1.06	0.59	0.35	0.072
Degree of calcification (mod/severe)	−0.67	0.65	0.51	0.30
Lesion grade (C vs. all others)	−0.51	0.58	0.60	0.39
ZoMaxx vs. Taxus	0.36	0.50	1.44	0.47
Vessel location (LAD vs. others)	−0.11	0.50	0.90	0.83
Pre-procedure MLD	0.12	0.78	1.13	0.88
Lesion length	−0.002	0.04	1.0	0.96
Multivariate				
Lesion location (ostial vs. others)	2.77	0.91	16.0	0.002
Diabetes	1.61	0.54	5.0	0.003

LAD = left anterior descending coronary artery; MLD = minimum lumen diameter; TVR = target vessel revascularization.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 5, 2008
OCTOBER 2008:524–32

between treatment groups for in-segment late loss was 0.27 mm (larger than the pre-specified 0.25 mm), the primary angiographic end point of noninferiority of in-segment late lumen loss was not met.

Given the differences in late lumen loss and the well-described curvilinear relationship of late loss to restenosis (25), it is not surprising that the ZoMaxx group was found to have statistically significantly higher rates of in-stent restenosis (12.9% vs. 5.7%; p = 0.025), as well as a trend toward increased ischemia-driven TLR as compared with Taxus (8.0% vs. 4.1%; p = NS). The specific mechanisms underlying these findings are speculative. The 2 stent systems differ in all critical design elements, including their stent platforms, drugs, pharmacological mechanisms of action, polymers, and formulations. The nondrug bare metal stent platforms seem to yield roughly comparable clinical and angiographic results, bearing in mind the relatively small patient cohorts subjected to rigorous angiographic follow-up (2,7,35). Both drugs have been shown to effectively inhibit mammalian cell proliferation in vitro and in animal models (29,41), and both have yielded variable clinical and angiographic results depending on their formulations, intervals of angiographic follow-up, and specific populations under study (range of in-stent late loss for paclitaxel-eluting stents: 0.30 to 0.81 mm [2,42–45]; zotarolimus-eluting stents: 0.12 to 0.67 mm [28,32,33,46]). It is noteworthy that the 9-month in-stent late lumen loss of patients treated with the ZoMaxx stent in this study (0.67 ± 0.57 mm) is strikingly similar to 8-month late lumen loss of patients treated with the Endeavor stent in each of Endeavor II (0.62 ± 0.46 mm) (28), Endeavor III (0.60 ± 0.48 mm) (33) and Endeavor IV (0.67 ± 0.49 mm) clinical trials (47). Thus, the prolonged release rate of ZoMaxx (24) as compared with Endeavor showed in nonconcurrent animal testing (4,24) had no apparent effect on results in humans. Interestingly, a zotarolimus-eluting stent using a different polymer formulation and having an even longer elution rate than ZoMaxx has recently been developed (Endeavor Resolute, Medtronic). Preliminary angiographic results in 30 patients suggest enhanced inhibition of neointimal hyperplasia using this formulation with a mean in-stent late loss of 0.12 ± 0.26 mm after 4 months (32). It can only be concluded that the efficacy of a given DES continues to be difficult to predict empirically and that long-term comparative clinical testing of each new formulation is required before its widespread application.

Conclusions

The ZoMaxx Coronary Stent can be safely implanted for the treatment of de novo coronary artery stenosis, as evidenced by the high rate of device implantation success (99%) and the low rates of subacute (0.5%) and late (0%) stent thrombosis. After 9 months, the ZoMaxx stent showed less neointimal inhibition than the Taxus stent, as demonstrated by higher in-stent late loss and restenosis by QCA and neointimal volume obstruction by IVUS.

Reprint requests and correspondence: Dr. Lewis B. Schwartz, Abbott Laboratories, 200 Abbott Park Road, AP52-2, Abbott Park, Illinois 60064-6215. E-mail: lewis.schwartz@abbott.com.

REFERENCES

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
3. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. Eurointervention 2006;2:286–94.
4. Kandzari DE, Leon MB. Overview of pharmacology and clinical trials program with the zotarolimus-eluting Endeavor stent. J Interv Cardiol 2006;19:405–13.
5. Benesh P. "Market for Drug-Eluting Stents Grows Crowded." *Investor's Business Daily*, November 2, 2007.
6. Lewis AL, Stratford PW. Phosphorylcholine-coated stents. J Long Term Eff Med Implants 2002;12:231–50.
7. Abizaid A, Popma JJ, Tanajura LF, et al. Clinical and angiographic results of percutaneous coronary revascularization using a trilayer stainless steel-tantalum-stainless steel phosphorylcholine-coated stent: the TriMaxx trial. Catheter Cardiovasc Interv 2007;70:914–9.
8. Hausleiter J, Kastrati A, Mehilli J, et al. Impact of lesion complexity on the capacity of a trial to detect differences in stent performance: results from the ISAR-STEREO trial. Am Heart J 2003;146:882–86.
9. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol 2003;41:1283–8.
10. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation 2001;103:2816–21.
11. Chen Y-W, Smith ML, Sheets M, et al. Zotarolimus, a novel sirolimus analogue with potent anti-proliferative activity on coronary smooth muscle cells and reduced potential for systemic immunosuppression. J Cardiovasc Pharmacol 2007;49:228–35.
12. Burke SE, Kuntz RE, Schwartz LB. Zotarolimus (ABT-578) eluting stents. Adv Drug Deliv Rev 2006;58:437–46.
13. Wagner R, Mollison KW, Liu L, et al. Rapamycin analogs with reduced systemic exposure. Bioorg Med Chem Lett 2005;15:5340–43.
14. Xue L, Sharma R, Cochran K, et al. The effect of the rapamycin derivative ABT-578 on canine smooth muscle cell and endothelial cell proliferation. Preclinica 2004;2:451–5.
15. Lewis AL, Cumming ZL, Goreish HH, Kirkwood LC, Tolhurst LA, Stratford PW. Crosslinkable coatings from phosphorylcholine-based polymers. Biomaterials 2001;22:99–111.
16. Campbell EJ, O'Byrne V, Stratford PW, et al. Biocompatible surfaces using methacryloylphosphorylcholine laurylmethacrylate copolymers. ASAIO J 1994;40:853–7.
17. Lewis AL, Tolhurst LA, Stratford PW. Analysis of phosphorylcholine-based polymer coating on a coronary stent pre- and post-implantation. Biomaterials 2002;23:1697–706.
18. Malik N, Gunn J, Shepherd L, Crossman DC, Cumberland DC, Holt CM. Phosphorylcholine-coated stents in porcine coronary arteries: in vivo assessment of biocompatibility. J Invasive Cardiol 2001;13:193–201.
19. Kuiper KK, Robinson KA, Chronos NAF, Cui J, Palmer SJ, Nordrehaug JE. Phosphorylcholine-coated stents in rabbit iliac and porcine coronary arteries. Scand Cardiovasc J 1998;32:261–8.
20. Whelan DM, van der Giessen WJ, Krabbendam SC, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart 2000;83:338–45.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 5, 2008
OCTOBER 2008:524–32

21. Zheng H, Barragan P, Corcos T, et al. Clinical experience with a new biocompatible phosphorylcholine-coated coronary stent. J Invasive Cardiol 1999;11:608–14.
22. Galli M, Bartorelli A, Bedogni F, et al. Italian BiodivYsio Open Registry (BiodivYsio PC-coated stent): study of clinical outcomes of the implant of a PC-coated coronary stent. J Invasive Cardiol 2000; 12:452–8.
23. Boland JL, Corbeij HAM, van der Giessen WJ, et al. Multicentre evaluation of the phosphorylcholine-coated BiodivYsio stent in short de novo coronary lesions: the SOPHOS study. Int J Cardiovasc Intervent 2000;3:215–25.
24. DuVall M, Ji Q, Clifford A, et al. ABT-578 elution profile and arterial penetration using the ZoMaxx drug-eluting stent (abstr). Am J Cardiol 2004;94:223E.
25. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV Trial. J Am Coll Cardiol 2005;45:1193–200.
26. Kereiakes DJ, Kuntz RE, Mauri L, Krucoff MW. Surrogates, substudies, and real clinical end points in trials of drug-eluting stents. J Am Coll Cardiol 2005;45:1206–12.
27. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
28. Fajadet J, Wijns W, Laarman G-J, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circulation 2006;114:798–806.
29. Garcia-Touchard A, Burke SE, Toner JT, Cromack K, Schwartz RS. Zotarolimus-eluting stents reduce experimental coronary artery neointimal hyperplasia after 4 weeks. Eur Heart J 2006;27:988–93.
30. Sakurai R, Hongo Y, Ormiston J, et al. First human experience with the ABT-578 eluting phosphorylcholine polymer stent: a serial volumetric intravascular ultrasound analysis (abstr). Abstract presented at: American College of Cardiology; March 8, 2004; New Orleans, Louisiana.
31. Abizaid A, Lansky AL, Fitzgerald PJ, et al. Percutaneous coronary revascularization using a trilayer phosphorylcholine-coated zotarolimus-eluting stent. Am J Cardiol 2007;99:1403–8.
32. Meredith IT, Worthly S, Whitbourn R, et al. The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Endeavor Resolute first-in-man trial. Eurointervention 2007; 3:50–3.
33. Kandzari DE, Leon MB, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. J Am Coll Cardiol 2006;48:2440–7.
34. Jain AK, Meredith IT, Lotan C, Rothman MT, Pateraki S. Real-world safety and efficacy of the endeavor zotarolimus-eluting stent: early data from the E-Five Registry. Am J Cardiol 2007;100:77M–83M.
35. Lasave LI, Costa JDR Jr, Abizaid AA, et al. A three-dimensional intravascular ultrasound comparison between the new zotarolimus-eluting stent (ZoMaxx) and the non-drug eluted TriMaxx stent. J Invasive Cardiol 2007;19:303–8.
36. Satler L. Aorto-ostial disease and aorto-ostial in-stent restenosis: poorly recognized but very complex lesion subsets. Catheter Cardiovasc Interv 2002;56:220–1.
37. Singh M, Gersh BJ, McClelland RL, et al. Predictive factors for ischemic target vessel revascularization in the prevention of restenosis with Tranilast and its outcomes (PRESTO) Trial. J Am Coll Cardiol 2005;45:198–203.
38. Huang HL, Hsieh IC, Chang SH, et al. Acute and long-term outcomes of intracoronary stenting in aorto-ostial, left anterior descending artery-ostial and nonostial stenoses. Int J Cardiol 2005;101: 391–7.
39. Lemos PA, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation 2004;109:1366–70.
40. Mavromatis K, Ghazzal Z, Veledar E, et al. Comparison of outcomes of percutaneous coronary intervention of ostial versus nonostial narrowing of the major epicardial coronary arteries. Am J Cardiol 2004;94:583–7.
41. Heldman AW, Cheng L, Jenkins GM, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation 2001;103:2289–95.
42. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003; 108:788–94.
43. Park SJ, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med 2003;348:1537–45.
44. Lansky AJ, Costa RA, Mintz GS, et al. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER Clinical Trial. Circulation 2004;109:1948–54.
45. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA 2005; 294:1215–23.
46. Meredith IT, Ormiston J, Whitbourn R, et al. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions: Endeavor I Trial. Eurointervention 2005;2:157–64.
47. Leon MB. Endeavor IV: a randomized comparison of a zotarolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease. Transcatheter Cardiovascular Therapeutics. October 22, 2007; Washington, DC.

Key Words: drug-eluting stent ■ stent ■ zotarolimus ■ restenosis ■ coronary artery disease.

APPENDIX

For a complete list of investigators and institutions, please see the online version of this article.

A Randomized, Controlled, Multicenter Trial to Evaluate the Safety and Efficacy of Zotarolimus- Versus Paclitaxel-Eluting Stents in De Novo Occlusive Lesions in Coronary Arteries: The ZoMaxx I Trial

Bernard Chevalier, Carlo Di Mario, Franz-Josef Neumann, Flavio Ribichini, Philip Urban, Jeffrey J. Popma, Peter J. Fitzgerald, Donald E. Cutlip, David O. Williams, John Ormiston, Eberhard Grube, Robert Whitbourn, Lewis B. Schwartz, for the ZoMaxx I Investigators

J. Am. Coll. Cardiol. Intv. 2008;1;524-532
doi:10.1016/j.jcin.2008.08.010

Coronary Artery Disease - Risk factors

Cardiovascular disease includes a number of conditions affecting the structures or function of the heart, including coronary artery disease and vascular (blood vessel) disease. Cardiovascular disease is by far the leading cause of death in the United States.

Who is affected by coronary artery disease?

Heart disease is the leading cause of death in the United States in men and women. Coronary artery disease affects 16.8 million Americans. The American Heart Association (AHA) estimates that about every 34 seconds, an will have a heart attack. In addition, the lifetime risk of having cardiovascular disease after age 40 is 2 in 3 men and more than 1 in 2 women.

Reference: Heart Disease and Stroke Statistics 2009 Update:
A Report from the American Heart Association Committee and Subcommittee. Circulation, 2009 January 27

Research about cardiovascular disease risk factors suggests that making even small lifestyle changes can reduce the risk of coronary artery disease, heart attack, stroke and other serious cardiovascular conditions.

What are the risk factors for coronary artery disease?

Risk factors are certain conditions that increase a person's risk for cardiovascular disease. It is important to know:

- Some risk factors, called " **nonmodifiable risk factors**," cannot be changed.
- Some risk factors, called " **modifiable risk factors**," can be modified, controlled or treated.
- The more risk factors you have, the greater your chance of developing cardiovascular disease.
- Higher levels of each risk factor correlate with a higher risk for cardiovascular disease.

Nonmodifiable risk factors

Check which ones apply to you

1. Increasing age

Cardiovascular disease is more likely to occur as you get older. About 85 percent of people who die of coronary artery disease are age 65 or older.

2. Male gender

Men have a greater risk of heart attack then women.

3. Menopause

After menopause, a woman's risk of cardiovascular disease increases, but does not reach the level of a man's.

4. Family history

Your risk of cardiovascular disease increases if your parents, brothers, sisters, or children have the disease.

5. Race

The risk of cardiovascular disease is higher in African Americans, Mexican Americans, American Indians, native Hawaiians and some Asian Americans. This increased risk is partly due to higher rates of high blood pressure, obesity and diabetes in these populations.

Since you can't change any of these risk factors, it is important to focus on the risk factors you **CAN** change.

Risk Factor Goals

You, along with support from your family and friends, can work to achieve the following goals to change or treat your modifiable risk factors and reduce your risk of cardiovascular disease. If you already have cardiovascular disease, you can follow these guidelines to help prevent its progression. (check which ones apply to you)

6. Stop smoking

- Smoking is the most preventable risk factor for cardiovascular disease and stroke.
- Smokers (including cigarette, pipe and cigar smokers) have more than twice the risk of a heart attack than nonsmokers.
- Smoking is also the biggest risk factor for sudden cardiac death. Even one to two cigarettes a day greatly increases the risk of heart attack, stroke and other cardiovascular conditions.
- Nonsmokers who are exposed to constant smoke also have an increased risk.

- **Goal:** Eliminate the use of all tobacco products. Stay away from other's smoke
  Learn more: Smoking and Heart Disease

7. Lower your total cholesterol, LDL (bad) cholesterol and triglyceride levels.

Excessive lipids (fatty substances including cholesterol and triglycerides), especially in the form of LDL cholesterol, cause the build-up of fatty deposits within your arteries, reducing or blocking the flow of blood and oxygen to your heart.

- There's a sharp increase in the risk for cardiovascular disease when total cholesterol levels are 240 mg/dl and above.

Goals: Total cholesterol less than 200 mg/dl

- **LDL cholesterol** should be less than 70 mg/dl for those with heart or blood vessel disease and other patients at very high risk of cardiovascular disease, such as those with metabolic syndrome. LDL cholesterol should be less than 100 mg/dl for those who have a high risk of cardiovascular disease, such as some patients with diabetes or those who have multiple heart disease risk factors. For all others, LDL cholesterol should be less than 130 mg/dl.
- **Triglycerides** less than 150 mg/dl.

It is recommended to have your cholesterol level checked as early as age 20 or earlier if you have a family history of high cholesterol. The cholesterol profile includes an evaluation of total cholesterol, HDL, LDL and triglyceride levels. Your health care provider can tell you how often to have your cholesterol tested.

8. Raise your HDL (good cholesterol).

HDL cholesterol takes the LDL (bad) cholesterol away from the arteries and back to the liver where it can be passed out of the body. High levels of HDL seem to protect against cardiovascular disease.

- **Goal :** HDL greater than 40 mg/dl; the higher the HDL level, the better.
  Learn more: Cholesterol Guidelines

9. Lower high blood pressure

Blood pressure is a measurement of the pressure or force inside your arteries with each heartbeat.

- High blood pressure increases the workload of the heart and kidneys, increasing the risk of heart attack, heart failure, stroke and kidney disease.
- High blood pressure is the biggest risk factor for stroke.

- **Goal :** 120/80 mmHg or lower (high blood pressure is 140/90 or higher)
  Control blood pressure through diet, exercise, weight management, and if needed, medications. Also limit alcohol, as it can increase your blood pressure.
  Learn more: Your Blood Pressure
  Learn more: Strategies to Control Blood Pressure

10. Control Diabetes

Diabetes occurs when the body is unable to produce insulin or use the insulin it has. This results in elevated blood sugar levels.

- People with diabetes (especially women) have a higher risk of cardiovascular disease because diabetes increases other risk factors, such as high cholesterol, LDL and triglycerides; lower HDL; and high blood pressure.
- Keeping diabetes under control is essential in reducing your risk.
- **Goal :** Hemoglobin A1c test less than 7.0% if you have diabetes, and less than 6.0% if you do not have diabetes. Follow-up with your doctor on a regular basis.
- Learn more: Cleveland Clinic Health Information Center

11. Maintain a healthy body weight

The more you weigh, the harder your heart has to work to give your body nutrients.

- Research has shown that being overweight contributes to the onset of cardiovascular disease.
- Excess weight also raises blood cholesterol, triglycerides and blood pressure, lowers HDL cholesterol and increases the risk of diabetes.
- How a person's weight is distributed also is important. People who carry their weight in the middle have a greater risk of developing cardiovascular disease, compared to people who carry their weight in their arms and legs. Waist measurements are one way to determine fat distribution.
- Weight is best determined by calculating Body Mass Index (BMI). BMI is a figure calculated from your height and weight. Doctors often use BMI as an objective indicator of whether a person is overweight, underweight, or at a healthy weight, and it is recommended by the National Institutes of Health for this purpose.

To calculate your BMI, divide weight in kilograms (kg) by height in meters squared (m2).
Metric conversions are: pounds divided by 2.2 = kg; inches multiplied by 0.0254 = meters.

For example, a woman who weighs 140 pounds and is 5 feet, 6 inches tall has a BMI of 23.
140 lbs divided by 2.2 = 64 kg
5'6" = 65" x 0.0254 = 1.65
1.652 = 2.72
64 divided by 2.72 = 23

Your health care provider can help you calculate your BMI.

- **Goals :** A normal BMI ranges from 18.5 to 24.9 kg/m^2. Overweight is defined as having a BMI higher than 25 kg/m^2. A BMI higher than 30 kg/m^2 is considered obese.
- Waist measurements for women should be less than 35 inches. Men should aim for a waist less than 40 inches.
- Achieve and maintain a desirable weight. A diet and exercise program will help you reach your goal.
  Learn more: Overweight and Heart Disease (includes BMI calculator)

12. Exercise

The heart is like any other muscle – it needs a workout to stay strong and healthy. Exercising helps improve how well the heart pumps blood through your body.

Activity and exercise also help reduce so many other risk factors: You can lower blood pressure, lower high cholesterol, reduce stress, achieve and maintain a healthy body weight, help yourself quit smoking and improve your blood sugar levels.

- **Goals :** Moderate exercise 30 minutes a day, on most days. More vigorous activities are associated with more benefits.
- Exercise should be aerobic, involving the large muscle groups. Aerobic activities include brisk walking, cycling, swimming, jumping rope and jogging. If walking is your exercise of choice, use the pedometer goal of 10,000 steps a day.
- Consult your doctor before starting any exercise program.
  Learn more: Exercise for your health

13. Follow a heart-healthy diet

The old saying, "You are what you eat," may be truer than ever - especially when it comes to cardiovascular disease. Four risk factors are related to diet: high blood pressure, high blood cholesterol, diabetes and obesity.

- **Goals :** Eat foods low in sodium, saturated fat, cholesterol, trans fat (partially hydrogenated fats) and

refined sugar.
- Omega-3 fatty acids are good fats and come from tuna, salmon, flaxseed, almonds, and walnuts. Mono-unsaturated fats also are preferred and are found in olive and peanut oils.
- Also eat plant-based foods such as fruit and vegetables, nuts and whole grains.
  Learn more: Nutrition Strategies

Contributing Risk Factors

Check which ones apply to you

Some risk factors are not considered traditional risk factors, but are still thought to contribute to overall risk for heart disease. These include:

14. Individual response to stress

Although stress is not considered a traditional risk factor, some researchers have noted a relationship between cardiovascular disease risk and stress in a person's life, their health behaviors and socioeconomic status. Stress may affect established risk factors.

Learn to manage stress by practicing relaxation techniques, learning how to manage your time, setting realistic goals, and trying some new techniques such as guided imagery, massage, Tai Chi or yoga.

15. Drinking too much alcohol

Intake of too much alcohol can lead to increased blood pressure, heart failure and stroke. It is also linked to high triglycerides, irregular heart beats, obesity, and cancer. Research has shown that those who drink one drink per day (4 oz. of wine, 12 oz. of beer, or 1– 1/2 oz. of 80-proof spirits) may have less risk. However, the American Heart Association does not recommend that non-drinkers start using alcohol or that drinkers increase the amount they drink.

Know your risk factors

If you have a family history of cardiovascular disease or high cholesterol, it is even more important to decrease your other risk factors. Get your cholesterol levels tested every year. Make sure you follow-up with your health care provider every year for a checkup.

- **Ask your doctor about the ultra-sensitive C-reactive protein (us-CRP) blood test.** High us-CRP levels are related to an increased risk of heart attack, stroke, peripheral vascular disease and restenosis (reclosing) of the arteries after angioplasty procedures.
- **Homocysteine is a protein in the blood. High levels of homocysteine** -- above 10 -- are associated with an increased risk of cardiovascular disease. There have been conflicting studies about the benefits and risks related to treatment of elevated homocysteine levels with folic acid and B vitamins. Therefore, ask your doctor before taking these supplements.
- Learn more about these laboratory tests

Resources:

To learn more about risk factors for heart and blood vessel disease

- Prevention
- American Heart Association website at www.americanheart.org *
- American Heart Association Heart Disease and Stroke Statistics *
- Risk Factors and Coronary Heart Disease, AHA Scientific Position*
- Stroke Risk Factors

Calculate your risk

The following risk factor assessment tools can be used to calculate your risk or make important treatment decisions:

- Framingham 10 year risk calculator
- Heart Profilers

These tools are designed to help you become more aware of your personal risk factors and to assist you in understanding treatment options. They are not meant to replace of the medical advice of your doctor or health care provider.

Here's to your heart-health!

The Preventive Cardiology and Rehabilitation Program at The Cleveland Clinic comprises a multi-disciplinary team of physicians, nurses, dietitians, exercise physiologists, and behaviorists. This team cares for people who either have heart disease or who are at risk. The program includes assessment, education, treatment and follow-up. A referral is required for an evaluation. Preventive Cardiology provides reports to your referring doctor on your treatment and progress.If you would like to be evaluated at the Cleveland Clinic for risk factors and current prevention strategies for cardiovascular disease, please use the Contact Us Form or contact the Preventive Cardiology and Rehabilitation Program at 216.444.9353 (or toll-free at 800.223.2273, extension 49353).

a new browser window will open with this link. The inclusion of links to other web sites does not imply any endorsement of the material on the web sites or any association with their operators

9500 Euclid Avenue, Cleveland, Ohio 44195 | 800.223.2273 | TTY 216.444.0261

CARDIOLOGY PATIENT PAGE

Restenosis: Repeat Narrowing of a Coronary Artery

Prevention and Treatment

George Dangas, MD; Frank Kuepper, MD

Angioplasty is a safe and effective way to unblock coronary arteries. During this procedure, a catheter is inserted into the groin or arm of the patient and guided forward through the aorta and into the coronary arteries of the heart. There, blocked arteries can be opened with a balloon positioned at the tip of the catheter. Initially, angioplasty was performed only with balloon catheters, but technical advances have been made and improved patient outcome has been achieved with the placement of small metallic spring-like devices called "stents" (Figure 1) at the site of the blockage. The implanted stent serves as a scaffold that keeps the artery open.

Angioplasty and stenting techniques are widely used around the world and provide an alternative option to medical therapy and bypass surgery for improving blood flow to the heart muscle. There are, however, limitations associated with angioplasty and stenting, one of which is called "restenosis."

What does restenosis mean?

Restenosis occurs when the treated vessel becomes blocked again. It usually occurs within 6 months after the initial procedure.[1] Compared with balloon angioplasty alone, where the chance of restenosis is 40%, stents reduce the chance of restenosis to 25%.[2,3] Therefore, the majority of patients having angioplasty today are treated with stents. Restenosis can occur after the use of stents, and physicians refer to this as "in-stent restenosis."

Why does in-stent restenosis happen?

When a stent is placed in a blood vessel, new tissue grows inside the stent, covering the struts of the stent. Initially, this new tissue consists of healthy cells from the lining of the arterial wall (endothelium). This is a favorable effect because development of normal lining over the stent allows blood to flow smoothly over the stented area without clotting. Later, scar tissue may form underneath the new healthy lining. In about 25% of patients, the growth of scar tissue underneath the lining of the artery may be so thick that it can obstruct the blood flow and produce an important blockage. In-stent restenosis is typically seen 3 to 6 months after the procedure; after 12 months have passed uneventfully, it is rare.

Who is at high risk for in-stent restenosis?

Patients with diabetes are at increased risk for in-stent restenosis. Further important risk factors relate to the properties of the blocked artery and the pattern of scar tissue growth inside the artery; the more extensive the scar tissue growth, the worse the prognosis is.[4]

What are the symptoms of in-stent restenosis?

In-stent restenosis may produce symptoms that are very similar to the symptoms that initially brought the patient to the interventional cardiologist, such as chest pain triggered by exertion. Diabetic patients, however, may have fewer symptoms, atypical and unusual symptoms, or even no symptoms at all. Fortunately, a heart attack does not usually occur even if in-stent restenosis develops.

How can we detect in-stent restenosis?

After stenting of coronary arteries, patients should follow-up with their cardiologist at regular intervals.

When symptoms occur after the procedure, the cardiologist may recommend diagnostic tests (for instance, an exercise stress test) to evaluate whether the patient is likely to have developed in-stent restenosis or another coronary artery is blocked. If in-stent restenosis is a possibility, the cardiologist may refer the patient for a repeat cardiac catheterization (Figure 2).

From the Cardiovascular Research Foundation, Lenox Hill Heart and Vascular Institute, New York, NY (G.D.), and Charité, Humboldt-University, Berlin, Germany (F.K.).

Correspondence to George Dangas, MD, PhD, Cardiovascular Research Foundation, Lenox Hill Heart and Vascular Institute, 55 East 59th Street, 6th Floor, New York, NY, 10022. E-mail gdangas@crf.org

(*Circulation.* 2002;105:2586-2587.)

***Circulation* is available at http://www.Circulationaha.org**
DOI: 10.1161/01.CIR.0000019122.00032.DF

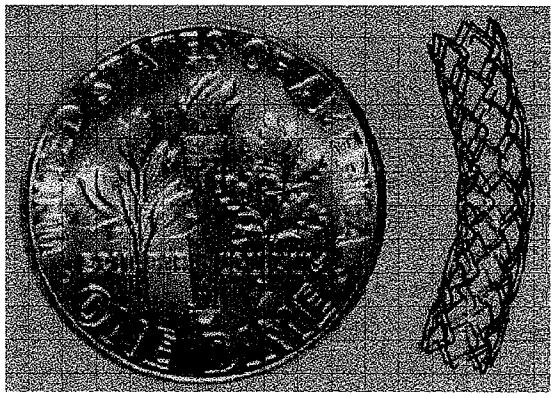


Figure 1. Size of an expanded coronary stent in relation to a dime. The stent is 18 mm in length and 3.5 mm in diameter.

Can in-stent restenosis be prevented?

Prevention of in-stent restenosis starts at the point of stent implantation. The physician's knowledge of appropriate stent placement is crucial. Some specialized centers may perform imaging with a special catheter from the inside of the vessel (ultrasound). This technique allows more accurate placement and expansion of stents[5] and may aid in the prevention of restenosis. Drugs and vitamins administered either orally or intravenously have been tested for prevention of restenosis and in-stent restenosis, but have not been consistently shown to be helpful.

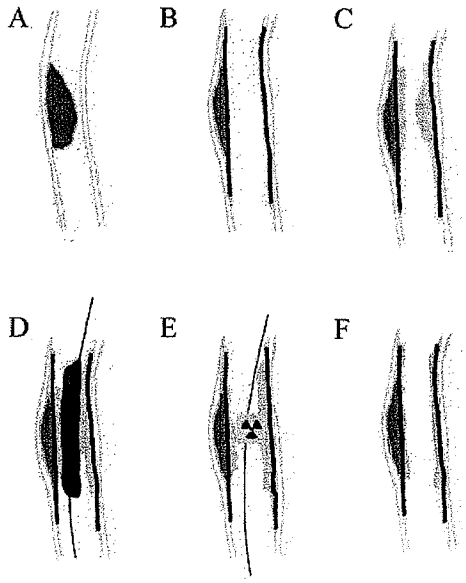


Figure 2. Development and treatment of in-stent restenosis. A, Coronary artery blocked by an atherosclerotic plaque. B, Unblocked coronary artery with an expanded stent. C, In-stent restenosis (scar tissue built up inside the stent). D, Balloon catheter in place to open coronary artery after occurrence of in-stent restenosis. E, Localized radiation therapy (brachytherapy) delivered to the location of in-stent restenosis by a special catheter to avoid recurrence of in-stent restenosis. F, Opened coronary artery after successful brachytherapy of in-stent restenosis. Drug-eluting stents prevent scar-tissue growth and may altogether obviate processes C through F.

New Techniques to Prevent Restenosis: Drug-Eluting Stents

During the last year, a breakthrough for the prevention of in-stent restenosis occurred in the form of a new generation of "drug-eluting" stents. These stents carry a special drug on their surface that prevents scar tissue growth in the artery where the stent is placed, and they therefore markedly reduce the occurence of in-stent restenosis. Recent data demonstrated that patients treated with drug-eluting stents had decreased incidence of in-stent restenosis compared with those who received bare metal stents.[6] Drug-eluting stents are not yet approved by the FDA, and the results of further studies are awaited.

How do we treat restenosis?

Repeat angioplasty or bypass surgery can be used to treat in-stent restenosis. In addition, local intravascular radiation (brachytherapy) can be used after treating in-stent restenosis with angioplasty to prevent reoccurrence.[7] Brachytherapy uses a radioactive source that is delivered by a coronary artery catheter inside the narrowed artery for a short period of time (about 10 minutes). The source is removed and does not stay in the body. Because the short period of radiation inhibits long-term tissue growth in the treated vessel, it successfully prevents in-stent restenosis. Both β- and γ-irradiation are helpful in this setting.[7] Only a few centers, however, have the special expertise needed to perform brachytherapy.

What can patients do to protect themselves?

After the procedure, patients should lead a heart-healthy lifestyle that includes a diet low in animal fat, regular exercise, blood pressure control, cessation of smoking, and minimal alcohol consumption. Regularly following-up with a cardiologist and taking medications as prescribed are also important preventive measures.

For additional discussion on in-stent restenosis, see www.heartcenteronline.com and www.tctmd.com.

References

1. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time- related phenomenon: a quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. *Circulation.* 1988;77:361–371.
2. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med.* 1994; 331:489–495.
3. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med.* 1994;331:496–501.
4. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation.* 1999;100:1872–1878.
5. Fitzgerald PJ, Oshima A, Hayase M, et al. Final results of the Can Routine Ultrasound Influence Stent Expansion (CRUISE) study. *Circulation.* 2000;102:523–530.
6. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation.* 2001;104: 2007–2011.
7. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med.* 2001;344:250–256.

Prostaglandins in the Cardiovascular System

Edited by

H. F. Sinzinger
K. Schrör

1992

Birkhäuser Verlag
Basel · Boston · Berlin

AAS 37
Prostaglandins in the
Cardiovascular System

EFFECTS OF CIPROSTENE ON RESTENOSIS RATE DURING THERAPEUTIC TRANSLUMINAL CORONARY ANGIOPLASTY

Harald Darius, Uwe Nixdorff, Johannes Zander,
Hans-Jürgen Rupprecht, Raimund Erbel and Jürgen Meyer

Department of Medicine II, Johannes Gutenberg - University,
Langenbeckstrasse 1, 6500 Mainz 1, Germany

SUMMARY

Ciprostene, a chemically stable prostacyclin analog was studied for its effects on restenosis in patients with coronary artery disease undergoing therapeutic percutaneous transluminal coronary angioplasty (PTCA). In a double-blind, randomized trial 32 patients were randomized to receive either ciprostene or the respective placebo. The infusion started intracoronarily at a rate of 40 ng/kg/min 20 min before introduction of the balloon catheter into the coronary artery. Thereafter infusion was continued intravenously for 36 hours at a rate of 120 ng/kg/min and a tapering off period until 48 hours. The quantitive analyses of the degree of coronary artery stenoses on the angiographic films before PTCA, after PTCA and after 6 month of follow-up was performed in 24 patients available.

In patients receiving placebo (n=12) coronary artery stenoses was 81±3 % before PTCA and was reduced to 34±3 % by angioplasty. At the 6 month follow up angiography stenoses diameter was measured as 63±8 %, being not significantly different from the % stenoses before PTCA. In contrast, coronary artery stenoses in patients receiving ciprostene (n=12) measured 83±3 % before PTCA, 31±4 % after PTCA and 55±9 % at 6 month, being still significantly different from pre-PTCA value ($P<0.05$). When patients were characterized according to their clinical status, these differences were accounted for by patients with unstable angina receiving ciprostene.

Ciprostene seems to reduce restenosis 6 month after coronary angioplasty in patients with unstable angina. The infusion rate of 40 ng/kg/min i.c. followed by 120 ng/kg/min i.v. was tolerated well, although the incidence of catheter associated bleedings was increased.

INTRODUCTION

Since introduction of percutaneous transluminal coronary angioplasty (PTCA) into clinical medicine this is the method of choice for the treatment of patients with coronary artery disease and high degree stenoses of proximal segments in one or two major arteries. One of the main clinical problems is the rate of restenoses during the 6 month period following the angioplasty. The studies performed to reduce the incidence of restenosis suggest, that treatment with platelet inhibitor drugs may reduce the risk of acute thrombotic complications during or early after the angioplasty procedure, however no effective medication for the prevention of restenosis after PTCA was reported (Corcos etal, 1985; Schwartz etal, 1988).

The mechanism of restenosis seems to involve initial platelet adherence at the site of balloon dilatation and in a second phase growth of fibroblasts and vascular smooth muscle cells. Platelets are able to release vasoconstrictor and proaggregatory mediators like TXA_2 or serotonin resulting in vasoconstriction, spasm, and acute thrombotic occlusions. Additionally, platelets release chemotactic mediators like 12-HETE stimulating smooth muscle cell movement and mitogens like PDGF (platelet derived growth factor) inducing smooth muscle cell proliferation. Therefore, effective inhibitors of platelet activation like PGI_2 may be able to prevent early vessel occlusion and late restenosis following PTCA.

This study was designed as a double-blind, randomized and placebo controlled trial to evaluate the effects of the chemically stable PGI_2 analog ciprostene (Linet etal, 1986) on restenosis rate in 32 patients undergoing therapeutic PTCA.

STUDY DESIGN AND METHODS

Study design and patient recruitment

The study was designed to compare the effects of ciprostene to placebo in patients undergoing single vessel PTCA. The design was randomized and double-blind. Main endpoint was the percent stenoses of the coronary artery dilated at the 6 month follow-up coronary angiography.

All 32 patients recruited for this study (25 males, 7 females; mean age 52.8 $\pm$ 8,6 yrs, range 31-68 yrs) were referred to our center for a balloon angioplasty of a coronary artery stenoses and gave their written informed consent. Patients with recent myocardial infarction, recent cerebrovascular accidents, known bleeding disorders, poorly controlled diabetes or arterial hypertension as well as premenopausal women were not included in this trial.

Patients were classified as suffering from unstable angina when anginal attacks occurred spontaneously and ECG changes typical of ischemia like ST-segment alteration or T-wave

inversion had been documented during the anginal attacks.

Coronary angiography, balloon dilatation and drug administration

Coronary angiography was performed according to the Judkins technique using a 9F guiding catheter. The catheter was introduced into the coronary artery to be dilated and the infusion of ciprostene or placebo was started intracoronarily at a dose of 40 ng/kg/min for 20 min. Immediately after termination of the intraarterial infusion an intravenous infusion at a rate of 40 ng/kg/min was started. Infusion rate increased by 20 ng/kg/min every 30 min, until a final infusion rate of 120 ng/kg/ min was administered, which was maintained for 36 hrs. In order to avoid the development of a rebound phenomenon, the infusion rate was tapered off by 20 ng/kg/min every two hrs until cessation of infusion 48 hrs after the angioplasty procedure.

Balloon angioplasty was performed immediately after termination of the intracoronary infusion using balloons of 2.0 to 3.5 mm in diameter. The coronary artery to be dilated was visualized by injection of contrast medium in two orthogonal views, which were chosen identical before and after PTCA and at the 6 month follow up angiography. For measurement of luminal diameters cine films were analyzed from a twentyfold magnified projection. Vessel contours were outlined manually using an ultrasonic pen and analyzed by a computer system (Cardiograph 200, Kontron Instruments). The degree of obstruction was calculated as the mean of the narrowest segments of all projections, in which the stenotic segment was clearly visible (Meyer etal, 1982).

Concomitant medication

All patients received aspirin (100 mg/d) and nifedipine (3 x 20 mg/d) as a local routine medical therapy until the follow up angiography at 6 month. During the PTCA procedure patients received organic nitrates, calcium antagonists, and heparin (10000 IU i.v. and 3000 IU i.c.). Patients with unstable angina were treated with aspirin and continuous infusion of heparin (15 IU/kg) additionally.

Miscellaneous

The study protocol was reviewed and approved by the institutional ethical committee (Ethikkommission bei der Ärztekammer Rheinland- Pfalz). The study was supported by The Upjohn Company, Kalamazoo, Michigan, USA.

All data presented are mean ± SEM of n observations. Longitudinal statistical analyses was performed by analysis of variance (ANOVA), means were compared by Student's t-Test for paired data using a commercially available computer program (Primer of Biostatistics, McGraw-Hill, New York, 1988).

RESULTS

Thirty two patients were recruited for the study and received ciprostene (n=17) or placebo (n=15). Final assessment including analyses of the three coronary angiography films before, after PTCA and at 6 month follow up was performed in 24 patients with successful PTCA (12 ciprostene, 12 placebo). In 4 patients with unstable angina (3 ciprostene, 1 placebo) plasma CK levels rose to more than twice the normal level indicating myocardial ischemia and a non successful dilatation, three patients rejected 6 month follow up coronary angiography, and one patient (placebo) underwent bypass surgery within 48 hrs after PTCA because of a large intimal dissection but without any signs of acute ischemia.

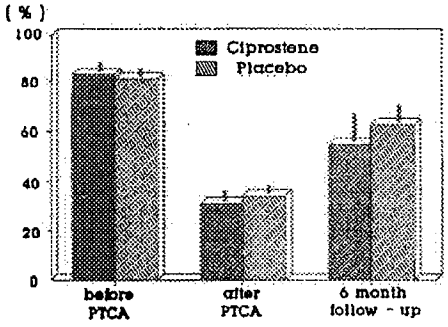
With respect to medical history and cardiovascular risk factor profile both groups of patients were comparable and did not show any significant differences.

Coronary angiography at 6 month

The alterations in the degree of coronary artery stenoses after PTCA and during the 6 month follow up in all patients are depicted in Figure 1. In patients receiving ciprostene stenoses diameter was reduced from 83±3 to 31±4 % by the PTCA procedure and increased to 55±9 % at 6 month. This follow up result in the ciprostene group is still significantly different to the situation before PTCA (P=0.012). The initial success of coronary artery dilatation was identical in patients receiving placebo, in which stenoses were reduced from an initial value of 81±3 % to 34±3 % after PTCA. At the 6 month follow up stenoses diameter had increased to 63±8 %. The patients in the placebo group did not exert any statistically significant difference in stenoses at the 6 month follow-up, when compared to the initial value (Fig. 1). There are no statistically significant differences in the degree of stenoses when the two groups are compared at a given time.

Figure 1

Degree of coronary artery stenoses in all patients with stable and unstable angina treated with ciprostene (n=12) or placebo (n=12).

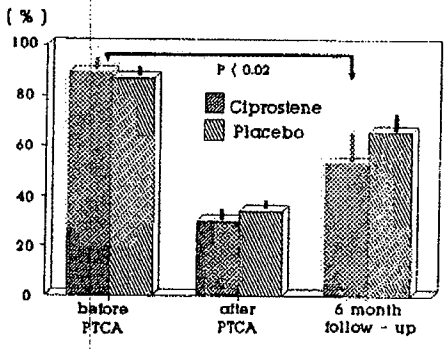


According to the clinical and electrocardiographic criteria given above 13 patients (6 ciprostene, 7 placebo) were classified as having unstable angina and 11 patients suffered from

stable angina (6 ciprostene, 5 placebo). Only patients with unstable angina receiving ciprostene exerted a significant difference at the 6 month follow-up coronary angiography when compared to the percent of stenoses before PTCA (Fig. 2). There is no hint, that infusion of ciprostene in patients with stable angina improves the angiographic outcome at 6 month.

Figure 2

Degree of coronary artery stenoses in patients with unstable angina treated with ciprostene (n=6) or placebo (n=7).



Hemodynamic drug effects

When patients receiving ciprostene were compared to the placebo group there were no statistically significant alterations in systolic or diastolic arterial blood pressure or heart rate during the infusion period.

Unwanted drug effects during the infusion period

The unwanted effects possibly related to the study medication are depicted in table 1. The number of puncture site hematomas was significantly higher in the ciprostene group (n=4) when compared to placebo (n=0). One ciprostene patient developed a bleeding from the groin after removal of the pressure cuff at a time, when ciprostene infusion had been terminated already. This patient received one unit of washed red blood cells and the further course was without any other complications. It is remarkable, that no non-catheter associated bleedings occurred.

Table 1
Unwanted events possibly related to the study medication

	Placebo (n=12)	Ciprostene(n=12)
Puncture site hematoma	0	4
Bleedings requiring transfusion	0	1
Facial flush	3	6
Headache	4	2
Nausea	2	2
Vomiting	2	1
Restlessness	1	1

Discussion

A number of studies were performed to identify alterations in medical therapy after PTCA in order to decrease the rate of restenoses. These studies included the use of platelet inhibitors (Schwartz etal, 1988), calcium antagonists (Corcos etal, 1985) or nitrovasodilators with platelet inhibitory effects like molsidomine (Darius etal, 1987). In 1990 Gershlick etal reported of a study on intravenous prostacyclin which did not show major beneficial effects. Despite of the multitude of trials undertaken to decrease restenosis significantly, no major breakthroughs were reported yet. The therapeutic approach tested in this study was the use of intracoronary and intravenous infusion of the prostacyclin analog ciprostene. In addition to inhibiting platelet aggregation PGI_2 reduces the release of mitogens like platelet derived growth factor (PDGF) from activated platelets (Stürzebecher etal, 1989). Thus, the administration of ciprostene during the PTCA procedure was performed in order to reduce the initial platelet deposition and platelet activation during angioplasty and thereby diminishing the risk of early thrombosis and late restenosis.

The angiographic analyses of the coronary artery stenoses in the two groups of patients studied did not show statistically significant differences between the two groups before PTCA and immediately thereafter. Thus, PTCA resulted in a comparable reduction in percent stenoses (Fig. 1). However, in patients receiving ciprostene stenoses at the 6 month follow up angiography was significantly lower when compared to the situation before PTCA (55 ± 9 vs 83 ± 3 %; $P=0.012$). This prolonged beneficial effect of the angioplasty procedure is due to the ciprostene infusion in patients with unstable angina. In patients with stable angina ciprostene had no detectable effect (Fig. 2).

The number of catheter associated hematomas at the puncture site was higher in the ciprostene group. Thus, during the infusion of prostacyclin analogs special attention should be paid to the concomitant medication with antiplatelet and anticoagulatory drugs.

In conclusion, in this study recruiting a limited number of 32 patients, angiographic analyses of the coronary artery stenoses hints to a possible beneficial effect of ciprostene in patients with unstable angina. Thus, further studies involving a larger cohort of patients are needed.

REFERENCES

Corcos, T., David, P.R., Val, P.G. etal (1985) Failure of diltiazem to prevent restenosis after percutaneous transluminal coronary angioplasty. Am. Heart J. 109, 926-931.

Darius, H., Rupprecht, H.J., Erbel, R., Pop, T., Brennecke, R., Meyer, J. (1987) A randomized study of pharmacologic prevention of coronary reocclusion after therapeutic PTCA.
Europ.Heart J. 8 (Suppl.2), 224.

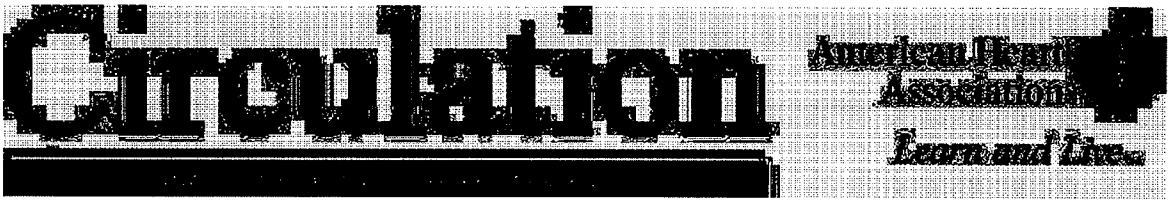
Gershlick, A.H., Timmis, A.D., Rothman M.T., Layton C.A., Balcon, R. (1990) Post angioplasty prostacyclin infusion does not reduce the incidence of restenosis. Circulation 82 (Suppl.III), 1974.

Linet, O.I., Nishizawa, E.E., Schaub, R.G., van der Lugt, J.T., Greenwald, C.A. (1986) Tolerance and pharmacology of ciprostene, a stable epoprostenol (prostacyclin) analogue in humans. J.Clin.Pharmacol. 26, 131-140.

Meyer, J., Merx, W., Schmitz, H., et al (1982) Percutaneous transluminal coronary angioplasty immediately after intracoronary streptolysis of transmural myocardial infarction. Circulation 66, 905-913.

Schwartz, L., Bourassa, M.G., Lesperance, J. et al (1988) Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty.
N.Engl.J.Med. 318, 1714-1719.

Stürzebecher, S., Nieuweboer, B., Matthes, S., Schillinger, E. (1989) Effects of PGD_2, PGE_1, and PGI_2-analogues on PDGF release and aggregation of human gel-filtered platelets. In: Prostaglandins in Clinical Research. Cardiovascular System (K. Schrör and H. Sinzinger, Eds) Alan R.Liss, New York, pp 365-370.



Clinical Efficacy of Polymer-Based Paclitaxel-Eluting Stents in the Treatment of Complex, Long Coronary Artery Lesions From a Multicenter, Randomized Trial: Support for the Use of Drug-Eluting Stents in Contemporary Clinical Practice

Keith D. Dawkins, Eberhard Grube, Giulio Guagliumi, Adrian P. Banning, Krzysztof Zmudka, Antonio Colombo, Leif Thuesen, Karl Hauptman, Jean Marco, William Wijns, Jeffrey J. Popma, Joerg Koglin, Mary E. Russell and on behalf of the TAXUS VI Investigators

Circulation 2005;112;3306-3313; originally published online Nov 14, 2005;
DOI: 10.1161/CIRCULATIONAHA.105.552190
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Clinical Efficacy of Polymer-Based Paclitaxel-Eluting Stents in the Treatment of Complex, Long Coronary Artery Lesions From a Multicenter, Randomized Trial

Support for the Use of Drug-Eluting Stents in Contemporary Clinical Practice

Keith D. Dawkins, MD; Eberhard Grube, MD; Giulio Guagliumi, MD; Adrian P. Banning, MD; Krzysztof Zmudka, MD; Antonio Colombo, MD; Leif Thuesen, MD; Karl Hauptman, MD; Jean Marco, MD; William Wijns, MD; Jeffrey J. Popma, MD; Joerg Koglin, MD; Mary E. Russell, MD; on behalf of the TAXUS VI Investigators

Background—Intracoronary polymer-based stent delivery of paclitaxel has been shown to be effective in reducing restenosis in simple coronary lesions, but the evidence base for contemporary use in longer, more complex coronary stenoses is lacking.

Methods and Results—TAXUS VI is a prospective, multicenter, double-blind, randomized trial assessing clinical and angiographic outcomes of the TAXUS Moderate Release paclitaxel-eluting stent in the treatment of long, complex coronary artery lesions. Four hundred forty-eight patients at 44 sites were randomized (1:1) between a drug-eluting TAXUS Express^2 and an uncoated Express^2 control stent. Per protocol, the 9-month follow-up included an angiographic reevaluation in all patients. The primary end point was the rate of target-vessel revascularization 9 months after the study procedure; secondary end points included the rate of target-lesion revascularization and binary restenosis at follow-up. Mean lesion length in the study was 20.6 mm, with a mean stent-covered length of 33.4 mm. Of all lesions, 55.6% were classified as complex lesions (type C of the AHA/ACC classification). At 9 months, target-vessel revascularization was 9.1% in the TAXUS group and 19.4% in the control group (P=0.0027; relative reduction, 53%). Target-lesion revascularization was reduced from 18.9% to 6.8%, respectively (P=0.0001). The incidence of major adverse cardiac events was similar in the 2 groups, 16.4% and 22.5% in TAXUS and control, respectively (P=0.12), including comparable rates for acute myocardial infarction. Binary restenosis in the stented area was reduced from 32.9% in the control group to 9.1% in the TAXUS patients (P<0.0001).

Conclusions—The finding that the TAXUS Moderate Release stent system is safe and effective in the treatment of long, complex coronary artery lesions provides the evidence base for the more widespread use of drug-eluting stents in contemporary clinical practice. (***Circulation.*** **2005;112:3306-3313.)**

Key Words: coronary artery disease ■ drugs ■ stents ■ restenosis ■ paclitaxel

Percutaneous intervention with intracoronary stents is now the most common procedure used in the invasive treatment of the patient with coronary heart disease. In previously published randomized clinical studies evaluating simple de novo coronary artery lesions, drug-eluting stents providing local drug delivery at the time of stent implantation reduced indices of restenosis, including the need for reintervention, compared with bare metal stents.[1–9]

Because of these promising results, paclitaxel- and sirolimus-eluting stents have become widely used in clinical practice, expanding beyond the simple lesions evaluated in clinical studies to more complex lesions and procedures. Contemporary use of this new technology in the treatment of the long, complex coronary stenoses commonly seen in clinical practice is lacking an evidence base. This randomized study was specifically designed to assess the safety and

Received March 28, 2005; revision received July 20, 2005; accepted July 22, 2005.

From Southampton University Hospital, Southampton, UK (K.D.D.); Krankenhaus Siegburg, Siegburg, Germany (E.G.); Ospedali Riuniti di Bergamo, Bergamo, Italy (G.G.); John Radcliffe Hospital, Oxford, UK (A.P.B.); Jan Pawel II Hospital, International Cardiology Clinic, Krakow, Poland (K.Z.); Ospedale San Raffaele, Milano, Italy (A.C.); Skejby Sygehus Hospital, Aarhus, Denmark (L.T.); Krankenhaus der Barmherzigen Brüder, Trier, Germany (K.H.); Clinique Pasteur, Toulouse, France (J.M.); O.L.V. Hospital, Aalst, Belgium (W.W.); Brigham and Women's Hospital, Boston, Mass (J.J.P.); and Boston Scientific Corp, Natick, Mass (J.K., M.E.R.).

Guest Editor for this article was James T. Willerson, MD.

The online-only Data Supplement, which lists study recruiting centers as well as members of the Clinical Events Committee and Data Safety and Monitoring Board, can be found at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.552190/DC1.

Correspondence to Keith D. Dawkins, MD, FRCP, FACC, Wessex Cardiac Unit, Southampton University Hospital, Southampton SO16 6YD, UK. E-mail keith@dawkins.org

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.105.552190**

efficacy of the polymer-based paclitaxel-eluting stents in patients with longer lesions often requiring the implantation of longer or multiple overlapping stents.

Methods

Paclitaxel-Eluting Stent System

The TAXUS stent consists of a balloon-expandable Express² stent with a triblock copolymer coating containing paclitaxel (1 μg/mm² of paclitaxel [loaded drug/stent surface area]). The Translute polymer coating poly(styrene-*b*-isobutylene-*b*-styrene) serves as a carrier to provide uniform and controlled biphasic release of the drug into the vessel wall once the stent is deployed. Slow- and moderate-release (MR) formulations of the polymer have been under investigation. The slow-release formulation is currently commercially available. The MR polymer formulation used in this study produces a paclitaxel release rate approximately threefold higher than the slow-release formulation on the basis of in vivo preclinical measurements. The TAXUS MR stent is premounted on a high-pressure monorail delivery catheter. An uncoated Express² stent (hereafter referred to as the control stent) served as the control in the study.

Patient Selection

Patients, who had to be at least 18 years of age, provided written informed consent and had to have evidence of myocardial ischemia and be eligible for percutaneous coronary intervention and acceptable candidates for coronary artery bypass grafting. Angiographic inclusion criteria included a de novo target lesion located within a single native coronary vessel with a reference vessel diameter between 2.5 and 3.75 mm, a cumulative target-lesion length of 18 to 40 mm, and a diameter stenosis ≥50%. Target lesions randomized to treatment with the study device had to be completely coverable by up to 2 study stents (maximum allowable stent length, 48 mm). Only 1 target lesion could be randomized and treated with a study stent(s) during the study procedure. To ensure a more "real-world" patient population, the study also allowed inclusion of patients with successful treatment of an additional uncomplicated nonstudy lesion located in a nontarget vessel before randomization during the same procedure.

Important exclusion criteria included recent acute myocardial infarction, poor left ventricular function, left main coronary artery disease, an ostial target-lesion location, total occlusion, or involvement of a bifurcation with a side branch diameter >2.0 mm. Treatment with additional devices (eg, cutting balloons, directional/rotational atherectomy) was not permitted.

Study Procedure

The study was approved by the local medical ethics committees at each of the investigation sites. Patients who met the study entry criteria were randomized to receive treatment with the TAXUS stent or the control stent using an interactive voice response system. Randomization schedules using a pseudorandom number generator were stratified by clinical site and by the presence or absence of medically treated diabetes mellitus. Within each stratum, eligible patients were randomized in a 1:1 ratio to receive either the TAXUS stent or the control stent. Study devices were packaged and labeled appropriately to maintain double-blind treatment assignments.

Patients were pretreated with aspirin 75 mg and clopidogrel 300 mg (at least 2 hours earlier). A dose of intravenous unfractionated heparin was administered that was sufficient to maintain the activated coagulation time ≥250 seconds. Intracoronary nitrates (glyceryl trinitrate or isosorbide dinitrate) were given before the baseline and final angiograms were recorded. Percutaneous intervention was undertaken by use of standard techniques; balloon predilatation before stent insertion was mandated. Intracoronary stents were implanted according to the manufacturer's instructions for use. Angiographic images were recorded according to the protocol of the angiographic core laboratory. A predischarge ECG was obtained, and cardiac enzyme estimations were taken 12 to 24 hours after stent placement. Aspirin ≥75 mg/d and clopidogrel 75 mg/d were continued for a minimum of 6 months after the procedure. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the physician.

Follow-Up

All enrolled patients were evaluated at 1, 3, 6, and 9 months after the stent implantation procedure; follow-up at 1, 2, 3, 4, and 5 years after the study procedure is planned. At the 9-month follow-up, an ECG was recorded, and an assessment was made of drug compliance, together with repeat coronary angiography. The study was considered complete (with regard to the primary end point) after all enrolled patients had completed the 9-month angiographic follow-up.

Data Management

Site monitoring and data management and analysis were undertaken by an independent organization (PPD Development, Nuernberg, Germany); after unblinding, the investigators had unrestricted access to the data. An independent core angiographic laboratory (Brigham and Women's Hospital Angiographic Core Laboratory, Boston, Mass) analyzed the angiograms without knowledge of the patient allocation. All major adverse cardiac events were reviewed and adjudicated by an independent committee whose members were unaware of the patients' treatment allocation. A Data Monitoring Committee periodically reviewed blinded safety data.

Study End Points

The primary end point of the study was the rate of target-vessel revascularization (TVR) 9 months after the study procedure. Secondary end points included the rates of clinical procedural success, composite major adverse cardiac events (MACE) (death, myocardial infarction, or target-lesion revascularization [TLR] and TVR) at 1, 3, 6, and 9 months after the study procedure and annually for 5 years, the target-vessel failure rate, and the stent thrombosis rate. Myocardial infarctions were categorized as Q-wave and non–Q-wave; Q-wave infarction was defined as the development of new pathological Q waves in 2 or more leads lasting 0.4 seconds or more with postprocedure creatine kinase (CK)-MB levels elevated above normal; non–Q-wave infarction was defined as the presence of postprocedure CK levels >2.0 times normal with positive CK-MB.

Quantitative Coronary Angiographic Analysis

Angiographic variables derived from 9-month restudy included absolute lesion length, stent length, reference vessel diameter, minimum lumen diameter, percent diameter stenosis, binary restenosis rate, acute gain, late loss, loss index, and the patterns of recurrent restenosis, including the edge effect (ie, measurements of the in-stent segment and the analysis segment, that is, the in-stent segment plus 5 mm at either end).

Statistical Analysis

The primary objective of the study was to evaluate the clinical safety and efficacy of the TAXUS stent in reducing the rate of ischemia-driven TVR in patients with de novo coronary lesions at 9 months. The null hypothesis was that the TVR rate in the treatment group would be equal to the TVR rate in the control group (H_0: $P_e - P_c = 0$), where P_e and P_c are the 9-month TVR rates for the treatment and control groups, respectively. The alternative hypothesis was that the TVR rate in the treatment group would be different from the TVR rate in the control group (H_1: $P_e - P_c \neq 0$). The calculation of the sample size (n=448) was based on a z test of equal proportions (normal approximation to binomial) at the 2-sided 5% significance level and 80% power. A 50% treatment effect was determined to be clinically significant assuming a control rate of 20%.

All analyses were based on the intention-to-treat principle. For continuous variables, differences between the treatment groups were evaluated by ANOVA or Wilcoxon's rank-sum test, as appropriate. For discrete variables, differences were expressed as counts and percentages and were analyzed with Fisher's exact test. Revascularization of the target lesion or vessel and the composite of major adverse cardiac events were also analyzed by the Kaplan-Meier

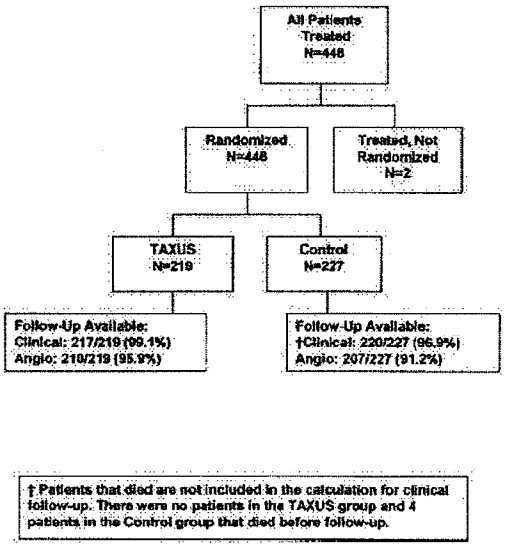


Figure 1. Patient flow.

method. Differences between the event-free survival curves for the 2 groups were compared with the use of log-rank tests.

Results

Baseline Characteristics

Between May and December 2002, 448 patients were enrolled at 44 sites in 15 European countries. Two patients who were treated with study stents without randomization (because of technical problems with the interactive voice-response randomization system) were excluded from the intent-to-treat analysis. Four hundred forty-six patients were randomized to receive a paclitaxel-eluting TAXUS Express^2 (n=219) or an uncoated bare-metal Express^2 control stent (n=227) (Figure 1). Patients were well matched for baseline demographics (Table 1) and lesion and vessel characteristics (Table 2) between the 2 groups. The mean lesion length was 20.6 mm, and the mean stent-covered length was 33.4 mm. Complex (American College of Cardiology/American Heart Association [ACC/AHA] type C) lesions were present in 55.6% of lesions, small-vessel (<2.5 mm in diameter) disease was present in 27.8%, overlapping stents were used in 27.8% of patients, and additional non–target-vessel percutaneous coronary intervention with a nonstudy stent was undertaken in 23.5% of patients.

Clinical Outcomes

The primary end point for the study was met in that the rate of TVR at 9 months was reduced from 19.4% (44 of 227) in the control group to 9.1% (20 of 219) in the TAXUS group (relative reduction, 53%; P=0.0027) (Figure 2). TLR was reduced from 18.9% (43 of 227) in the control group to 6.8% (15 of 219) in the TAXUS group (relative reduction, 64%; P=0.0001). The TLR benefit with TAXUS was independent of the classic risk factors for restenosis; in small vessels (<2.5 mm in diameter), 29.7% and 5.0% (relative reduction, 83%; P=0.0003); in long lesions (≥26 mm), 26.3% and 4.4% (relative reduction, 83%; P=0.0097); in diabetics, 22.0% and 2.6% (relative reduction, 88%; P=0.0103); and in patients with multiple, overlapping stents, 23.0% and 1.6% (relative reduction, 93%; P=0.0002) for the control and TAXUS groups, respectively.

Safety Outcomes

Stent thrombosis occurred in 3 of 227 patients (1.3%) in the control group and 1 of 219 patients (0.5%) in the TAXUS group (P=NS) during the 9-month study period. No patient suffered a stent thrombosis in the 3-month period after cessation of the 6-month therapy with clopidogrel and the 9-month follow-up. Overall MACE (death, acute myocardial infarction, TVR) at 9 months was similar in the 2 groups at 22.5% and 16.4% in the control and TAXUS groups, respectively (P=0.12). The components of MACE and other clinical outcomes are detailed in Table 3.

Angiographic Outcomes

Follow-up 9-month angiography was available in 417 patients (93.5%), 210 of 219 (95.9%) of the TAXUS group and 207 of 227 (91.2%) of the control group (Table 4). Binary restenosis (rate of patients with % diameter stenosis in-stent >50% at follow-up) was reduced from 32.9% in the control

TABLE 1. Baseline Demographics and Clinical Characteristics

	TAXUS (N=219)	Control (N=227)	*P*
Baseline			
Age	61.8±9.7	63.4±9.9	0.09
Male, % (n/N)	76.3% (167/219)	76.2% (173/227)	1.00
Medically treated diabetes, % (n/N)	17.8% (39/219)	22.0% (50/227)	0.29
Insulin requiring, % (n/N)	6.8% (15/219)	8.8% (20/227)	0.48
Non–insulin requiring, % (n/N)	11.0% (24/219)	13.2% (30/227)	0.47
Medically treated hyperlipidemia, % (n/N)	70.3% (149/212)	73.4% (163/222)	0.52
Medically treated hypertension, % (n/N)	57.5% (126/219)	58.1% (132/227)	0.92
Current smoker, % (n/N)	22.5% (47/209)	23.9% (52/218)	0.82
Unstable angina, % (n/N)	24.7% (54/219)	22.9% (52/227)	0.74
Previous PCI, % (n/N)	17.9% (39/218)	20.7% (47/227)	0.47

TABLE 2. Baseline Vessel and Lesion Characteristics

	TAXUS (N=219)	Control (N=227)	P
Baseline lesion characteristics			
Lesion length, mm	20.94±7.206	20.32±7.882	0.36
Reference vessel diameter, mm	2.81±0.488	2.77±0.464	0.41
Minimum lumen diameter, mm	0.84±0.345	0.87±0.332	0.39
Diameter stenosis, %	70.2±10.67	68.6±10.65	0.12
Target lesion vessel, % (n/N)			0.37
Left anterior descending coronary artery	53.4% (117/219)	47.1% (107/227)	
Circumflex	17.8% (39/219)	18.5% (42/227)	
Right coronary artery	28.8% (63/219)	34.4% (78/227)	
Lesion location, % (n/N)			0.40
Ostial	1.4% (3/219)	1.8% (4/227)	
Proximal	39.7% (87/219)	34.4% (78/227)	
Mid	55.3% (121/219)	57.3% (130/227)	
Distal	3.7% (8/219)	6.6% (15/227)	
Modified ACC/AHA classification, % (n/N)			0.77
A	0.9% (2/219)	0.4% (1/227)	
B1	15.1% (33/219)	16.7% (38/227)	
B2	26.5% (58/219)	29.1% (66/227)	
C	57.5% (126/219)	53.7% (122/227)	
Stents (in target vessel) per patient, % (n/N)			0.91
None	0.5% (1/219)	0.9% (2/227)	
1	59.8% (131/219)	61.2% (139/227)	
2	34.7% (76/219)	32.6% (74/227)	
≥3	5.0% (11/219)	5.3% (12/227)	
Maximum stent diameter implanted, mm	3.1±0.33 (218)	3.1±0.32 (225)	0.83
Total stent length implanted, mm	33.7±10.79 (218)	33.2±10.14 (225)	0.62
Total stent length-to-lesion length ratio	1.7±0.58 (216)	1.8±0.73 (224)	0.28
Maximum pressure overall, atm	15.3±2.82 (219)	15.2±2.66 (227)	0.88
Maximum balloon-to-artery ratio	1.1±0.21 (217)	1.1±0.20 (223)	0.23

Values are expressed as % (n/N) where indicated or as mean±SD.

group to 9.1% in the TAXUS patients (relative reduction, 72%; $P<0.0001$) (Figure 3, A–C). The TAXUS benefit in binary restenosis was independent of the classic risk factors for restenosis; in small vessels (<2.5-mm diameter) 40.4% and 7.3% (relative reduction, 82%; $P<0.0001$), in long lesions (≥26-mm), 50.0% and 7.0% (relative reduction, 86%; $P<0.0001$), in diabetics 40.5% and 8.1% (relative reduction, 80%; $P=0.0015$), and in patients with multiple, overlapping

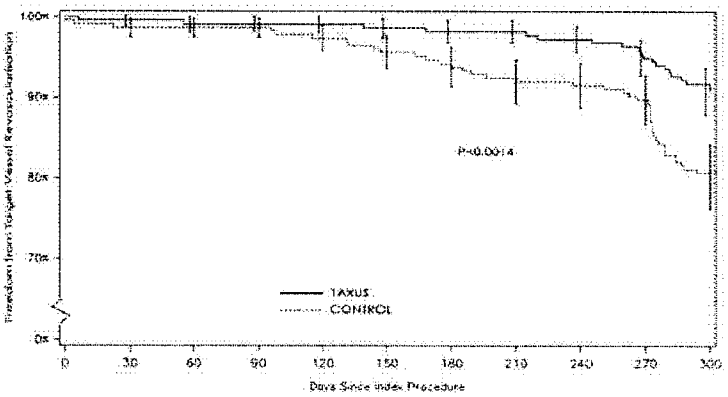


Figure 2. Freedom from TVR to 300 days; intent-to-treat, event-free survival ±1.5 SEM, all patients (N=446).

TABLE 3. Clinical Outcomes

	TAXUS (N=219), % (n/N)	Control (N=227), % (n/N)	P
In-hospital MACE			
MACE, overall	6.8% (15/219)	4.8% (11/227)	0.42
Cardiac death	0.0% (0/219)	0.4% (1/227)	1.00
MI	6.8% (15/219)	4.0% (9/227)	0.21
Q-wave MI	0.9% (2/219)	0.9% (2/227)	1.00
Non–Q-wave MI	5.9% (13/219)	3.1% (7/227)	0.17
TVR, overall	0.0% (0/219)	0.9% (2/227)	0.50
Target lesion revascularization, overall	0.0% (0/219)	0.9% (2/227)	0.50
PCI	0.0% (0/219)	0.4% (1/227)	1.00
CABG	0.0% (0/219)	0.4% (1/227)	1.00
TVR, nontarget lesion, overall	0.0% (0/219)	0.0% (0/227)	NA
30-Day MACE			
MACE, overall	7.3% (16/219)	5.3% (12/227)	0.44
Cardiac death	0.0% (0/219)	0.4% (1/227)	1.00
MI	7.3% (16/219)	4.0% (9/227)	0.15
Q-wave MI	0.9% (2/219)	0.9% (2/227)	1.00
Non–Q-wave MI	6.4% (14/219)	3.1% (7/227)	0.12
TVR, overall	0.5% (1/219)	1.3% (3/227)	0.62
Target lesion revascularization, overall	0.5% (1/219)	0.9% (2/227)	1.00
PCI	0.5% (1/219)	0.4% (1/227)	1.00
CABG	0.0% (0/219)	0.4% (1/227)	1.00
TVR, nontarget lesion, overall	0.0% (0/219)	0.4% (1/227)	1.00
9-Month MACE			
MACE, overall	16.4% (36/219)	22.5% (51/227)	0.12
Cardiac death	0.0% (0/219)	0.9% (2/227)	0.50
MI	8.2% (18/219)	6.2% (14/227)	0.46
Q-wave MI	1.4% (3/219)	1.3% (3/227)	1.00
Non–Q-wave MI	6.8% (15/219)	4.8% (11/227)	0.42
TVR, overall	9.1% (20/219)	19.4% (44/227)	0.0027
Target lesion revascularization, overall	6.8% (15/219)	18.9% (43/227)	0.0001
PCI	5.9% (13/219)	17.6% (40/227)	0.0001
CABG	0.9% (2/219)	1.8% (4/227)	0.69
TVR, nontarget lesion	3.2% (7/219)	0.9% (2/227)	0.10
Target-vessel failure rate, %	16.0% (35/219)	22.0% (50/227)	0.12
Stent thrombosis			
In-hospital	0.0% (0/219)	0.4% (1/227)	1.00
Out of hospital to 30 days	0.5% (1/219)	0.9% (2/227)	1.00
31 to 180 days	0.0% (0/219)	0.0% (0/227)	NA
181 to 300 days	0.0% (0/219)	0.0% (0/227)	NA

MACE indicates major adverse cardiac events; MI, myocardial infarction; and TVR, target-vessel revascularization;

stents 45.5% and 4.8% (relative reduction, 89%; $P<0.0001$) for the control and TAXUS groups, respectively.

Late lumen loss (reduction in minimum lumen diameter from after the procedure to follow-up) was reduced from 0.99 ± 0.59 to 0.39 ± 0.56 mm ($P<0.0001$) in stent and from 0.66 ± 0.62 to 0.24 ± 0.57 mm in the analysis segment (including the stented area plus the proximal and distal 5-mm edge, $P<0.0001$). Details of the continuous and binary 9-month quantitative angiographic results are presented in Table 4.

The length of in-stent restenosis in the TAXUS group was significantly shorter than in the control group at 10.8 ± 6.05 and 17.7 ± 9.72 mm, respectively ($P=0.0048$), with a significant shift to more focal restenosis in the TAXUS patients. At 9-month angiographic follow-up, late acquired aneurysms (defined as vessel distension ≥1.2 times reference vessel diameter present at follow-up but not after the procedure) were observed in 1 control patient (0.5%) and 3 TAXUS patients (1.4%) ($P=0.62$).

Discussion

The impact of coronary heart disease on the health economy is profound, and percutaneous coronary techniques have become the dominant treatment option, particularly because the advent of intracoronary stents has resulted in a predictably low periprocedural complication rate. The Achilles heel of bare-metal stent implantation has been the development of angiographic in-stent restenosis. After implantation of a bare-metal stent, there are a number of established predictors of restenosis, particularly lesion length and complexity, vessel diameter, and the presence of diabetes mellitus.[10] This prospective, multicenter, double-blind, randomized trial provides, for the first time, the evidence base for the treatment of patients with these risk factors. The population evaluated in this study is representative of patients presenting in current clinical practice and is the most challenging so far treated with drug-eluting stents, with lesion lengths >20 mm, implanted stent covered length 33.4 mm, overlapping stents used in 27.8%, complex (ACC/AHA type C) lesions present in 55.6% of lesions, small-vessel (<2.5-mm diameter) disease in 27.8%, and medically treated diabetes in 17.8%.

In this high-risk group, superior and concordant results were found for the TAXUS stent for clinical and angiographic measures of restenosis compared with the control bare stent. In-stent binary restenosis was reduced in the TAXUS group to 9.1% from 32.9% in the control patients ($P=0.0001$; relative reduction, 72%). Published trials assessing the angiographic response to bare-metal stents implanted in long lesions predict a binary restenosis rate of 39% to 45%,[11,12] comparable with bare-metal stents used in the control limb of the other published drug-eluting stent trials of simple lesions, for example, 36.7% in the RAVEL trial,[5] 35.4% in the SIRIUS trial,[6] and 42.3% in the E-SIRIUS trial.[7]

Despite the already favorable angiographic result with the control (Express^2) stent, there was an additional 53% reduction in TVR (the primary end point of the study) from 19.4% to 9.1% in the TAXUS group compared with control ($P=0.0027$). Thus, direct patient benefit for the reduced need for either redo percutaneous or surgical revascularization as a consequence of ischemia-driven restenosis of the study vessel is demonstrated for the TAXUS MR stent.

Safety in terms of MACE at 9 months was statistically similar in the 2 groups (16.4% and 22.5% in the TAXUS and control groups, respectively, $P=0.12$), Non–Q-wave myocardial infarction trended numerically higher in the TAXUS

TABLE 4. Quantitative Coronary Angiography

	TAXUS (N=219)	Control (N=227)	P
9-Month binary restenosis rate, % of patients			
In-stent	9.1% (19/209)	32.9% (68/207)	<0.0001
Analysis segment	12.4% (26/210)	35.7% (74/207)	<0.0001
Reference vessel diameter, mm			
Before procedure	2.81±0.488 (219)	2.77±0.464 (227)	0.41
After procedure	2.84±0.504 (219)	2.81±0.462 (226)	0.47
9-Month follow-up	2.83±0.443 (210)	2.74±0.466 (207)	0.0307
Minimum lumen diameter, mm (in-stent)			
Before procedure	0.84±0.345 (219)	0.87±0.332 (226)	0.39
After procedure	2.58±0.407 (218)	2.57±0.360 (225)	0.68
9-Month follow-up	2.20±0.604 (209)	1.58±0.661 (207)	<0.0001
Diameter stenosis, % (in-stent)			
Before procedure	70.2±10.67 (219)	68.6±10.65 (226)	0.12
After procedure	8.3±10.42 (218)	7.7±10.09 (225)	0.60
9-Month follow-up	22.2±19.15 (209)	42.8±20.90 (207)	<0.0001
Late loss, mm			
In-stent	0.39±0.560 (209)	0.99±0.585 (207)	<0.0001
Analysis segment	0.24±0.567 (210)	0.66±0.619 (207)	<0.0001
Proximal edge	0.16±0.538 (195)	0.33±0.532 (194)	0.0019
Distal edge	−0.02±0.407 (208)	0.11±0.365 (202)	0.0013

Values are expressed as % (n/N) where indicated or as mean±SD.

group at 9 months, reflecting the in-hospital non–Q-wave myocardial infarction rate associated with the index procedure (in-hospital non–Q-wave infarction 5.9%, 13 of 219; and 3.1%, 7 of 227, $P=0.17$, in the TAXUS group and control patients, respectively). In that lesion complexity in the 2 groups was well matched, the cause of this discrepancy remains unclear; possible explanations include an increase in side-branch compromise because of the (thicker) polymer-coated stent struts, a polymer-induced local response, and microembolization, among others.

Previous concerns relating to the possible association between thrombosis and drug-eluting stents have not been realized, with only a single stent thrombosis in the TAXUS group (0.5%) and 3 stent thromboses in the control group (1.3%) at 9 months (P=NS). Importantly, no stent thrombosis occurred in the 3-month period after clopidogrel had been discontinued when patients were maintained on low-dose aspirin alone, although this trial was not powered to investigate prospectively the incidence of stent thrombosis, which, with a frequency of ≈1%, would require a randomized trial of 10 000 to 20 000 patients.

Late-acquired aneurysms were not found significantly more frequently in the TAXUS group compared with control patients (1.4%, 3 of 209, versus 0.5%, 1 of 207, respectively; $P=0.62$), despite the higher local paclitaxel release from the TAXUS MR stent used in this trial compared with the TAXUS SR stent that has been assessed in earlier studies.[1–4] Further insights into aneurysm formation (including the question of inadequate or incomplete healing) are likely to be realized in the Taxus VI intravascular ultrasound substudy (n=179), which will be reported in detail elsewhere.

When the data become available, a comparison of the outcomes from the TAXUS V trial (using the SR formulation) will allow a detailed analysis of the efficacy and effect of the 2 paclitaxel dose formulations in similar patient subsets.

There was no deleterious "edge" effect in the TAXUS group, such that the relative reduction in binary restenosis was similar within the in-stent and the analysis segments (Figure 3).

The results of treatment in the predefined diabetic subgroup of 89 were very gratifying, with a reduction of in-stent binary restenosis from 40.5% in the control group to 8.1% in the TAXUS group ($P=0.0015$; relative reduction, 80%), which was consistent across the various diabetic subgroups regardless of medication, glycemic control, or severity of the disease.

Taken together, these findings support the National Institute for Clinical Excellence (NICE) guidance in the United Kingdom in relation to the clinical and cost effectiveness of stents (including drug-eluting stents),[13] who base their recommendations on angiographic indices, namely, a target-vessel diameter of <3.0 mm and a target-lesion length of >15 mm for the use of drug-eluting stents. It was suggested that these higher-risk lesion subsets may be present in one third of patients; more recent evidence shows that these characteristics are present in 77% of a population undergoing percutaneous treatment in a typical UK referral center.[14]

Before the advent of drug-eluting stents, operators used the shortest possible stents to treat the lesion (so called "spot" stenting) because of awareness that the likelihood of restenosis was related to the implanted stent length. This study

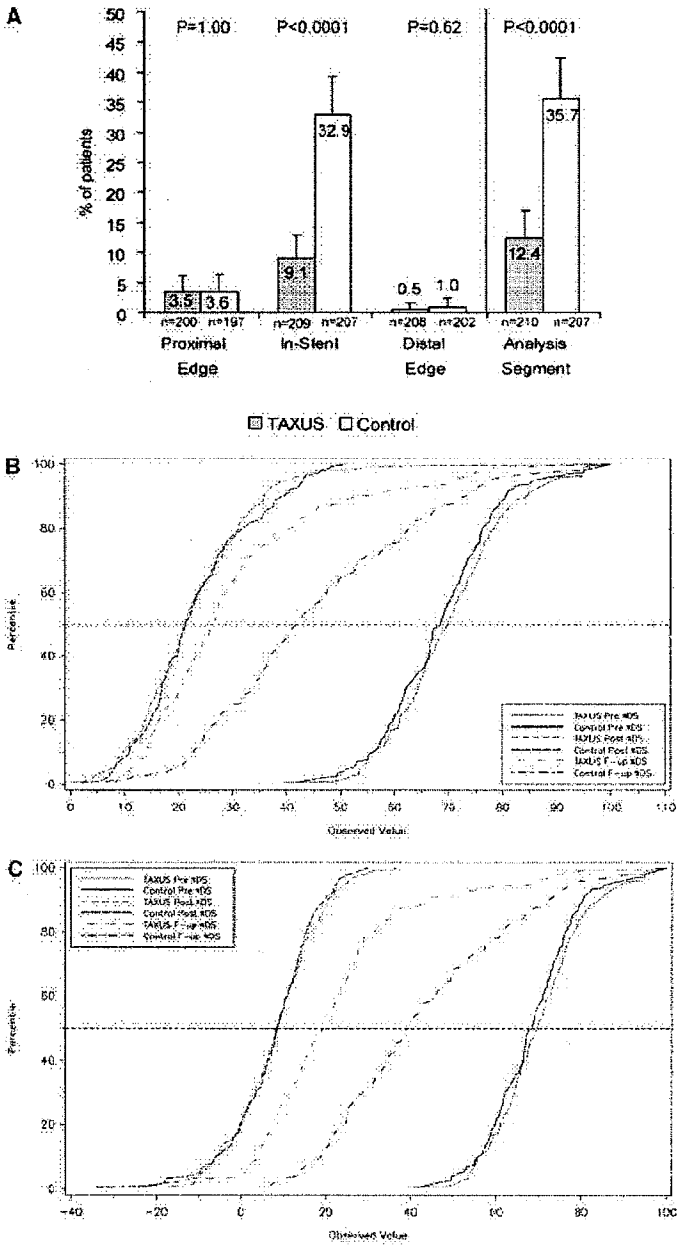


Figure 3. A, Binary restenosis rates in-stent and at the edges. B, Angiographic patency (cumulative frequency distribution of in-segment percent diameter stenosis by QCA; intent-to-treat, all patients (N=446). C, Angiographic patency (cumulative frequency distribution of in-stent percent diameter stenosis by QCA; intent-to-treat, all patients (N=446).

confirms the applicability of "stenting long" with a lesion-to-stent ratio of 1:1.7, thus stenting back to angiographically "normal" vessel on either side of the lesion without the penalty of late in-stent restenosis. In patients who did develop in-stent restenosis, the lesions were significantly shorter and more focal in the TAXUS group, thus facilitating further treatment with conventional percutaneous techniques.

Limitations of the study include the possibility of increasing the likelihood of developing in-stent restenosis in the control patients as a result of using a "stenting long" strategy. Also, although a clinical assessment of patient status was made before undertaking the 9-month angiogram, the "oculostenotic reflex" may have affected the TLR rate.

This study extends the applicability of drug-eluting stents beyond proof of concept studies[15] evaluating single, discrete lesion stenting by confirming the safety and efficacy of the TAXUS MR stent system in the treatment of long, complex coronary artery lesions, including small vessel diameter and multiple overlapping stents. Since the commercial availability of drug-eluting stents in Europe in 2002, percutaneous

intervention has become the most frequently used revascularization option; this study makes the decision making all the more rational.

Acknowledgments

This study was supported by Boston Scientific Corp.

Dr Keith D. Dawkins and Dr Eberhard Grube, as principal investigators, were responsible for the conception, design, and execution of the study, the analysis and interpretation of the data, and the writing of the manuscript. Drs Giulio Guagliumi, Adrian Banning, Krzysztof Zmudka, Antonio Colombo, Leif Thuesen, Karl Hauptman, Jean Marco, William Wijns, and Jeffrey J. Popma participated substantially in the enrollment of patients, execution of the study, and the review of the manuscript. Mary E. Russell and Joerg Koglin participated in the design and execution of the study, the analysis of the data, and the writing of the manuscript. All authors approved the final version of the report. Please see the Data Supplement for a list of recruiting centers and the members of the Clinical Events Committee and Data Safety Monitoring Board.

Disclosure

The study sponsor, Boston Scientific Corp, Natick, Mass, supported the design of the study and the collection and analysis of the data and participated in the writing of the report. Dr Dawkins is a consultant to Boston Scientific Corp, and Drs Russell and Koglin are employees and stockholders of Boston Scientific Corp, the sponsor of the study. Dr Guagliumi also has a consulting agreement with Boston Scientific. No other conflict of interest was declared by any coauthor of this article.

References

1. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation*. 2003;107:38–42.
2. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME, TAXUS II Study Group. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stent for coronary artery lesions. *Circulation*. 2003;108:788–794.
3. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Tift Mann J, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME, for the TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004;350:221–231.
4. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Tift Mann J, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME for the TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting stent: the TAXUS-IV trial. *Circulation*. 2004;109:1942–1947.
5. Morice M-C, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R, RAVEL Study Group. A randomized comparison of a sirolimus eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773–1780.
6. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE, SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315–1323.
7. Schofer J, Schlüter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G, for the E-Sirius investigators. Sirolimus-eluting stents for the treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet*. 2003;362:1093–1099.
8. Park S-J, Shim WH, Ho DS, Raizner AE, Park S-W, Hong M-K, Lee CW, Choi D, Jang Y, Lam R, Weissman NJ, Mintz GS. A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med*. 2003;348:1537–1545.
9. Gershlick A, De Scheerder I, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C, Reifart N, Missault L, Goy J-J, Brinker JA, Raizner AE, Urban P, Heldman AW. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaluation of paclitaxel eluting stent (ELUTES) trial. *Circulation*. 2004;109:487–493.
10. Ho KKL, Senerchia C, Rodriguez O, Chauhan MS, Kuntz RE. Predictors of angiographic restenosis after stenting: pooled analysis of 1197 patients with protocol mandated angiographic follow-up from five randomized stent trials. *Circulation*. 1998;98:362–368.
11. Hoffmann R, Herrmann G, Silber S, Braun P, Werner GS, Hennen B, Rupprecht H-J, vom Dahl J, Hanrath P, for the Impact Upon Long lesion Stenting Study Group (IMPULSE). Randomized comparison of success and adverse event rates and cost effectiveness of one long versus two short stents for treatment of long coronary narrowings. *Am J Cardiol*. 2002;90:460–464.
12. Oemrawsingh PV, Mintz GS, Schalij MJ, Zwinderman AH, Wouter Jukema J, van der Wall EE. Intravascular ultrasound guidance improves angiographic and clinical outcome of stent implantation for long coronary artery stenoses: final results of a randomized comparison with angiographic guidance (TULIP study). *Circulation*. 2003;107:62–67.
13. *Guidance on the Use of Coronary Artery Stents*. Technology Appraisal No. 71 (October 2003). National Institute for Clinical Excellence (NICE). http://www.nice.org.uk/pdf/TA71_coronaryarterystents_fullguidance.pdf.
14. Wells T, Dawkins KD. Drug eluting stents: NICE guidelines and the reality. 2005. *Br J Cardiol*. 2005;12:45–48.
15. Babapulle MN, Joseph L, Bélisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet*. 2004;364:583–591.